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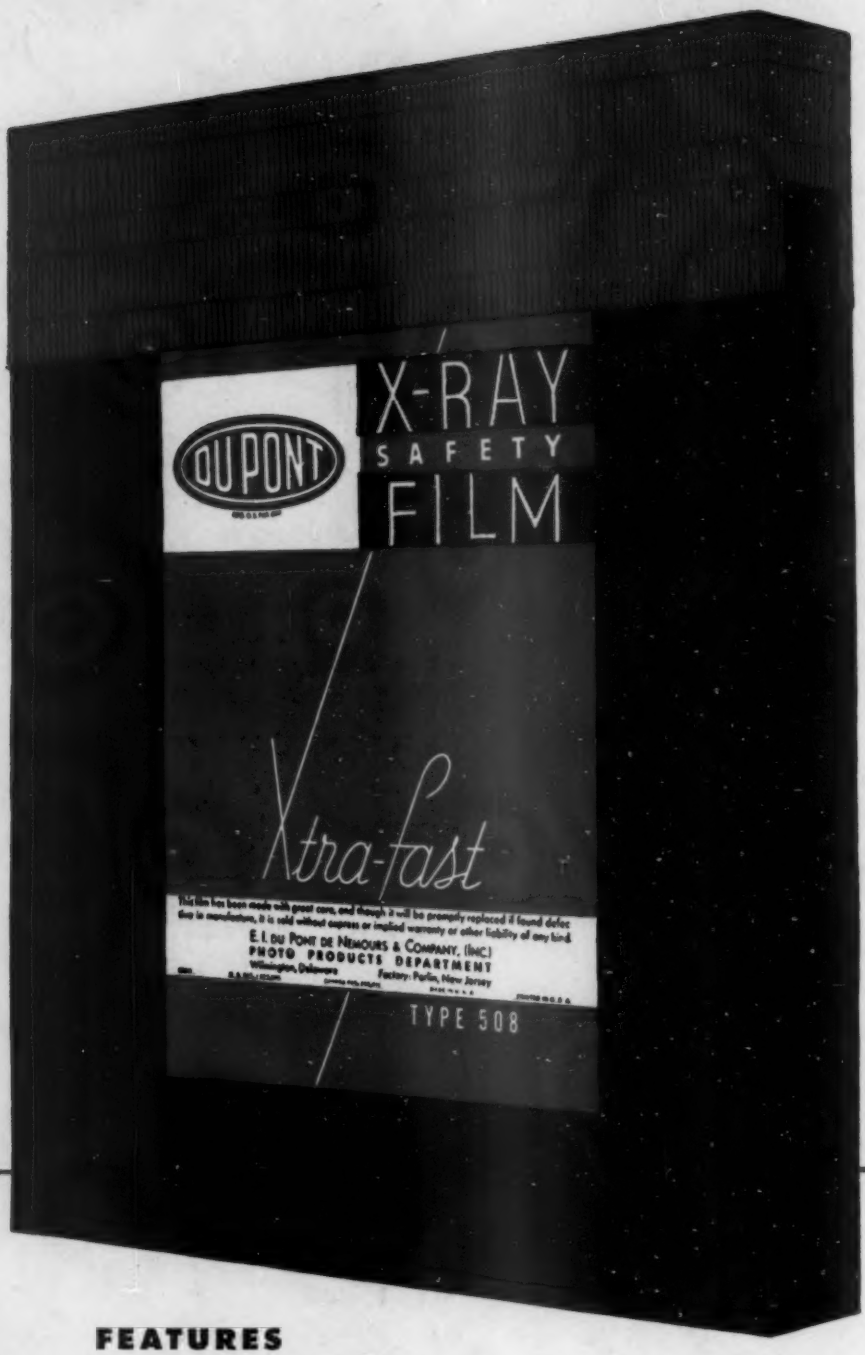

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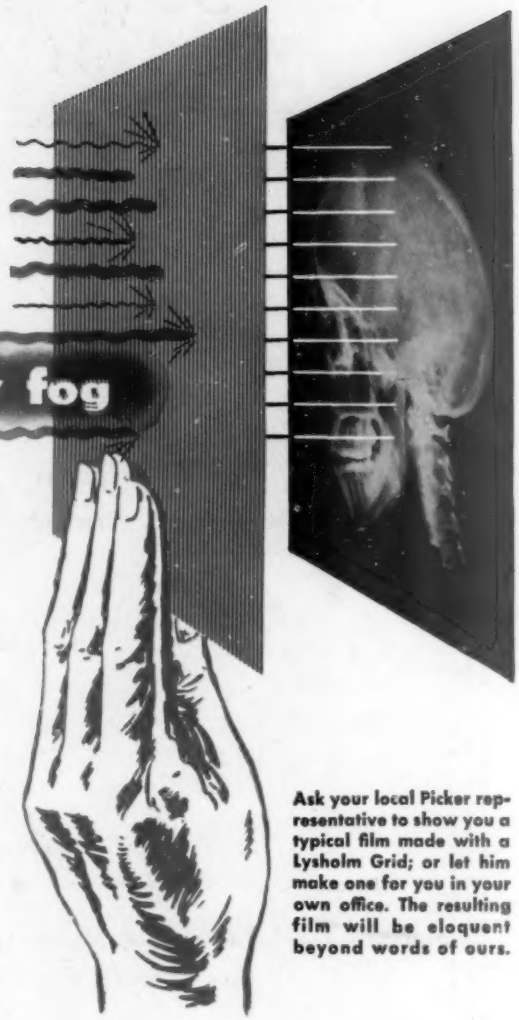

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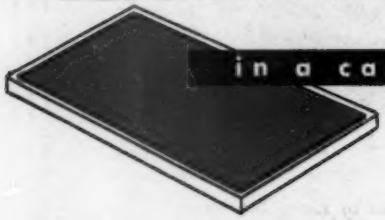

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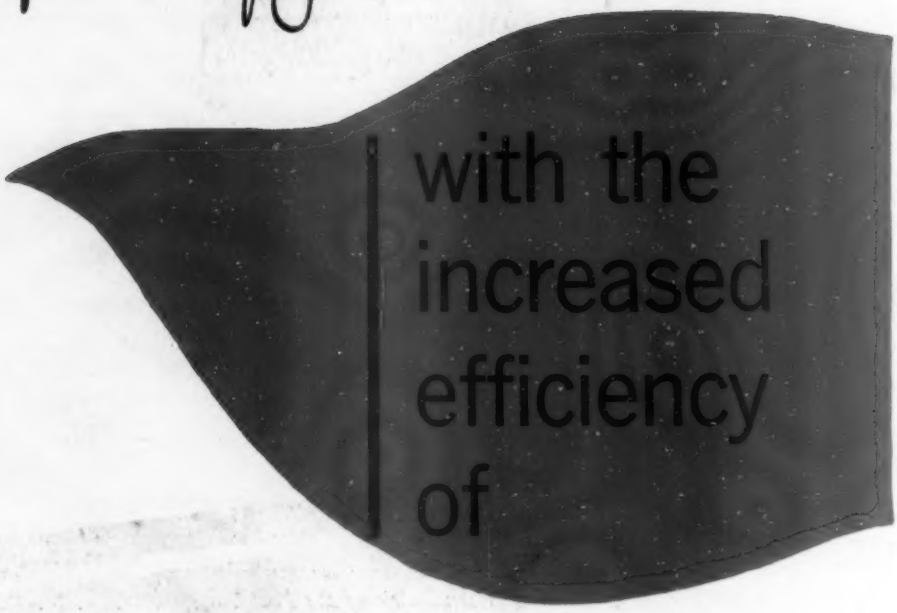

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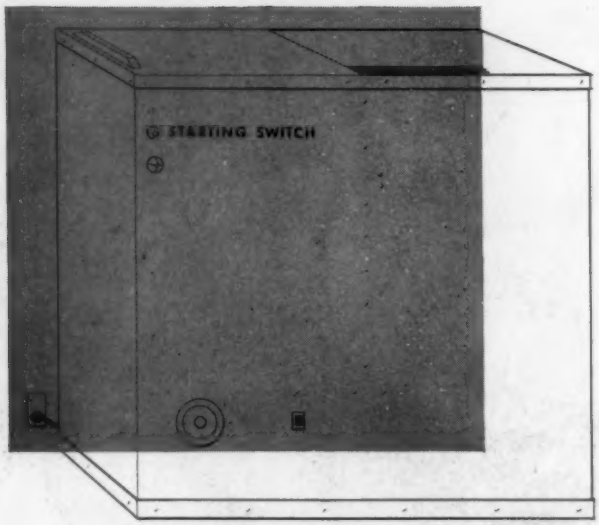

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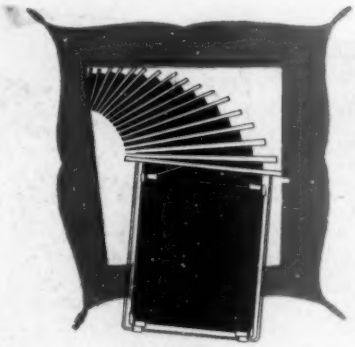

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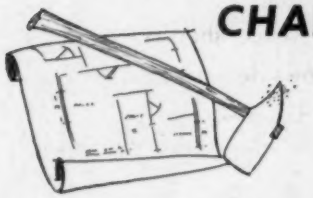

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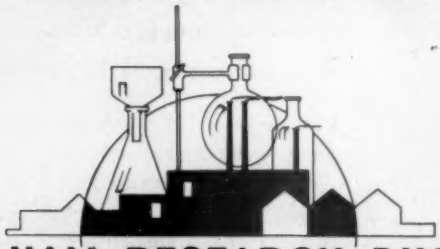

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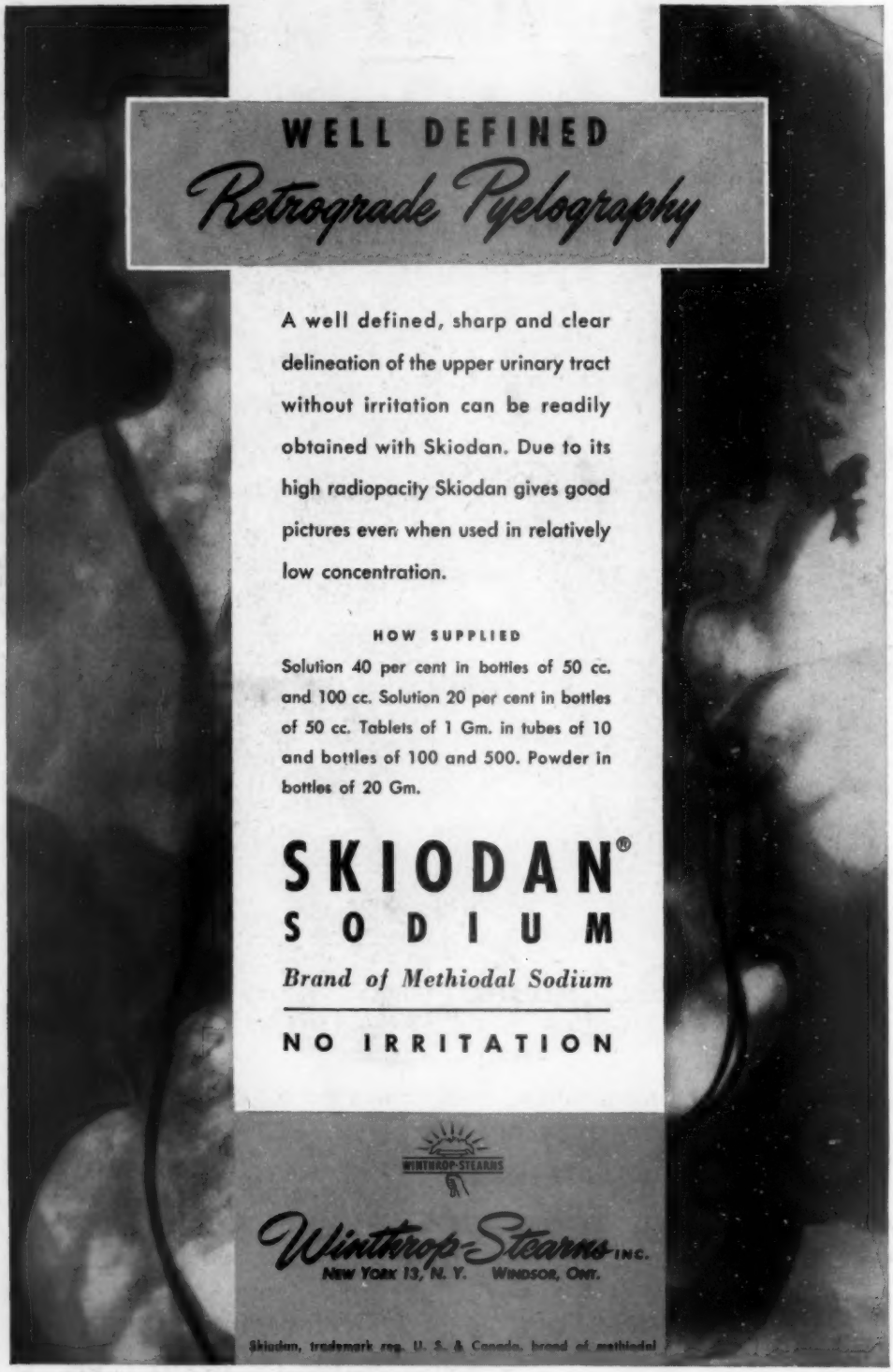
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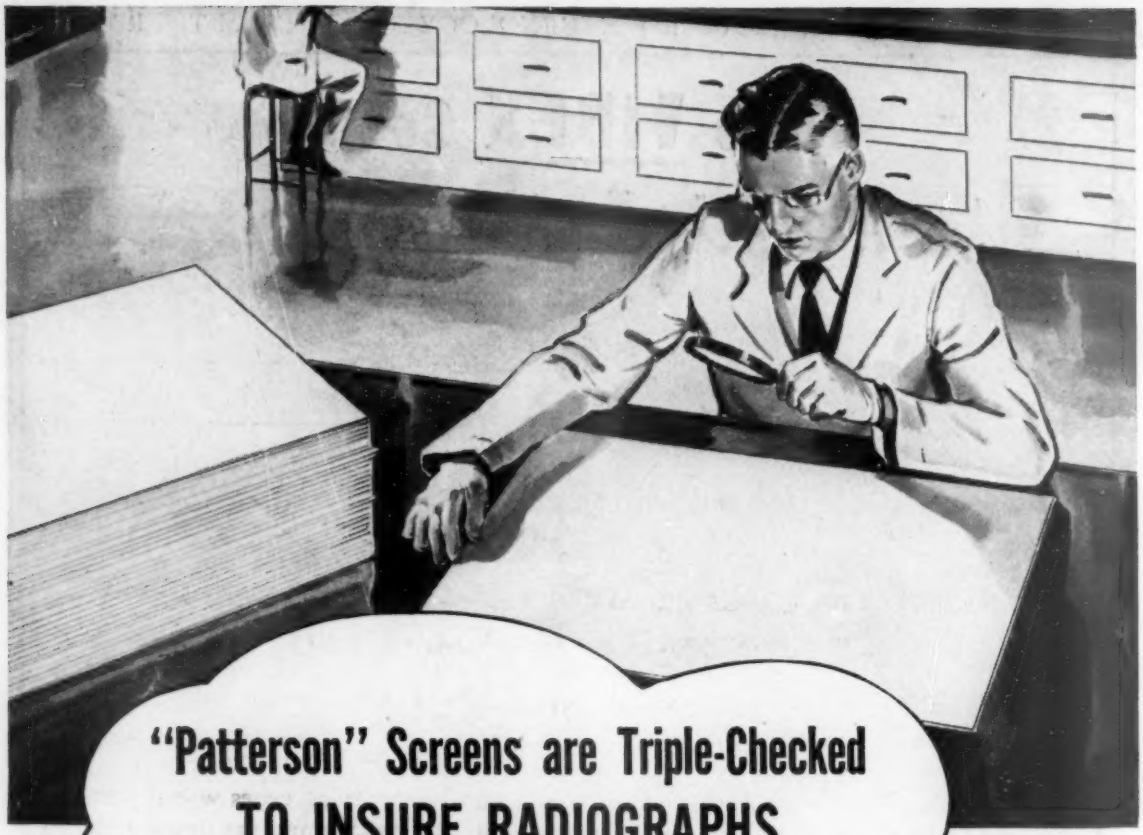

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VOL. 61 APRIL, 1949 No. 4

HEMOSIDEROSIS OF THE LUNG DUE TO MITRAL DISEASE

A REPORT OF SIX CASES SIMULATING PNEUMOCONIOSIS*

By EUGENE P. PENDERGRASS,† M.D., EDWIN L. LAME,** M.D.
and
HERMAN W. OSTRUM,‡ M.D.
PHILADELPHIA, PENNSYLVANIA

THIS report deals with mitral valve disease accompanied by the deposition of hemosiderin in the lungs, in such a fashion that roentgenograms reveal a fine nodulation much like pneumoconiosis or miliary tuberculosis. We have a thirteen year and a four month roentgen observation on 2 living patients carrying this lesion; and have found 4 autopsied cases of similar nature which provide the histopathologic explanation.

Such cases are very rare. From the United States there is no autopsied case reported; and from the world literature a total of 17 autopsied cases previous to those disclosed herein. Not all of the 17 demonstrated a clear granular roentgen pattern. Rosenhagen, in 1928, probably is the first to have described the roentgenology together with the histopathology. Since then, Pedro Pons and Amell Sans, Anglin, Munk, Roche, Scott, Park and Lendrum, and others,[12,33,41] have added to the meager record. Pendergrass and Leopold predicted that one of our living cases would prove to be such a lesion. Sosman has discovered one case with autopsy, which he is allowing us to report at this time.

Nodular lung lesions seen in roentgenograms and confirmed histopathologically as siderosis have been described in several categories. Arc welders may inhale iron-laden fumes to such an extent that lung roentgenograms reveal a diffuse nodular pattern caused by the deposition of the metal.[7,9,18,35] Silver finishers, working in rouge (iron oxide), are subject to a similar lung deposit of an iron compound.[20] Grinders of ferrous metal, not exposed to silica, have been shown[27] to carry a fine granular lung lesion, which appears roentgenographically very much as nodular silicosis. These three groups are examples of exogenous siderosis of the lungs.

Endogenous pulmonary siderosis is exemplified by our group of mitral heart disease patients and by the children who suffer severe anemias[2,8,28,39,40] and die with hemo-

* From the Departments of Radiology, Hospital of the University of Pennsylvania,† the Presbyterian Hospital of Philadelphia.** and the Philadelphia General Hospital.‡ Presented at the Forty-ninth Annual Meeting, American Roentgen Ray Society, Chicago, Ill., Sept. 14–17, 1948.

siderin nodules in the lungs. These lesions, too, have been demonstrated in roentgenograms.

Brown induration of the lung, resulting from hyperemia and congestion, accompanied by calcification and bone formation, is more often found in mitral disease.[11,13,14,34,42] The small irregular densities seen in such roentgenograms are due to the calcium or bone and not to iron compound.

All of the foregoing patients demonstrate diffuse nodular densities in lung roentgenograms that suggest miliary tuberculosis or the more common pneumoconioses.

REPORT OF CASES

Case 1. J. S. (Fig. 1 and 2), male, white, aged thirty-three. Interest in this subject was aroused by the discovery of this man's roentgenograms by one of us (E. P. P.) at the Hospital of the University of Pennsylvania. In 1931, at the age of sixteen, he spit blood. Rheumatic endocarditis was found. He had

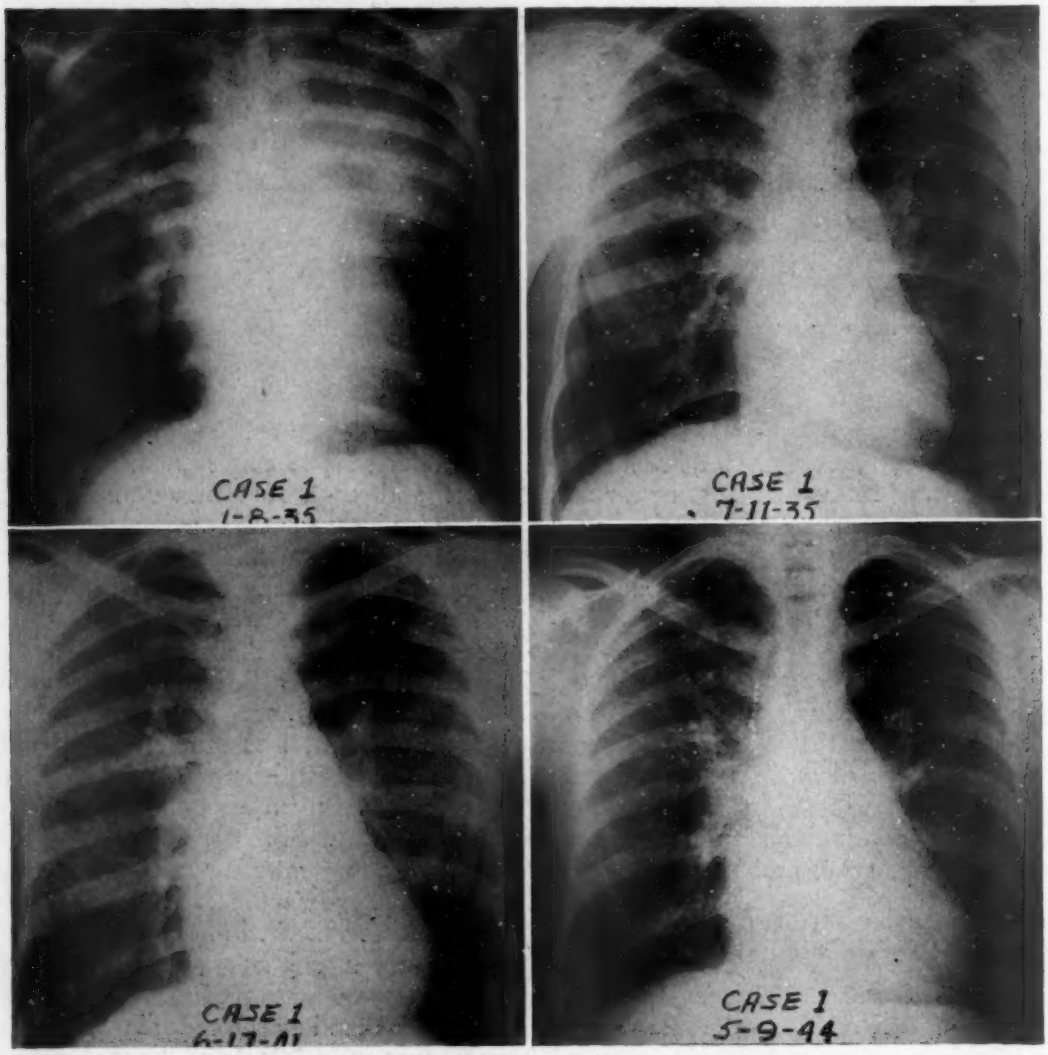

Fig. 1. Case 1. J. S. Representative roentgenograms from a thirteen year observation. Marked generalized nodulation present at first acquaintance when a pneumonia existed. Subsequent studies show an increased prominence of nodules and then a static condition, except for added cardiac enlargement.

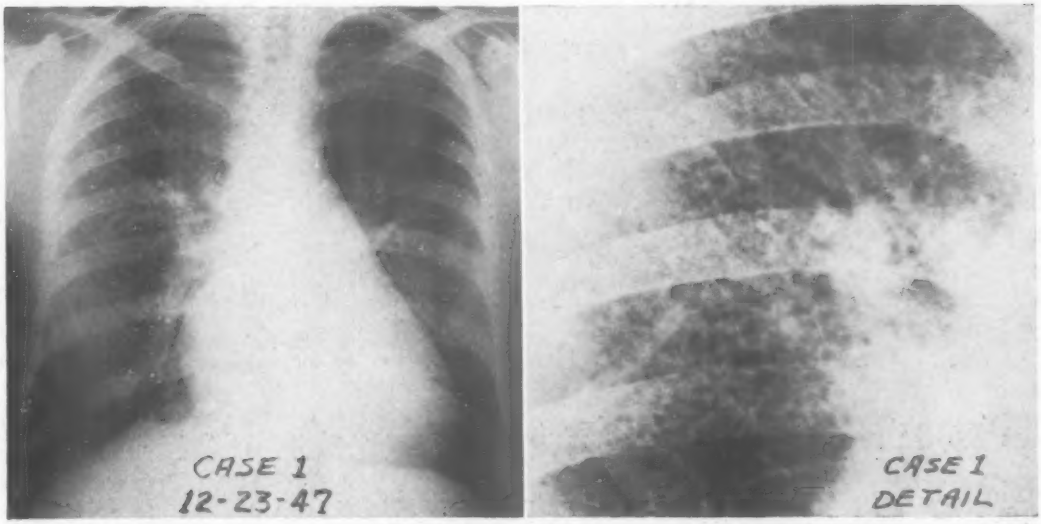

Fig. 2. Case 1. J. S. Continuation of Figure 1. The magnified portion of lung demonstrates the irregular, non-circular character of the fine lesion.

other attacks from 1932 to 1934 and in late 1934 suffered a type IV pneumococcus pneumonia, when his chest roentgenograms demonstrated a bilateral pneumonic lesion. At that time, there was a generalized nodular lesion in addition, which we believe antedated the acute disease. Since then, all studies have revealed this fine nodular pattern resembling miliary tuberculosis or pneumoconiosis. In 1935, a tuberculin skin test (0.01 mg.) was negative at forty-eight hours. After that he was followed by the cardiac clinic, except for eight years when he was too well to return. Roentgen studies were made whenever the patient was available from

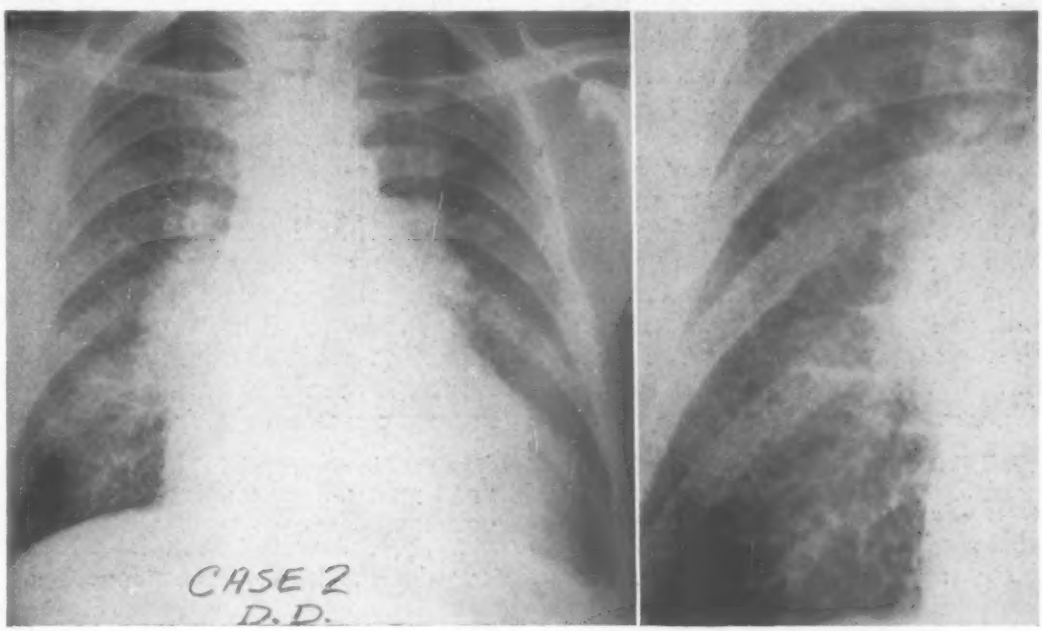

Fig. 3. Case II. D. D. Patient dying of rheumatic mitral heart disease, with autopsy diagnosis of pulmonary siderofibrosis. The nodules on the roentgenogram measure up to 3 mm. in diameter.

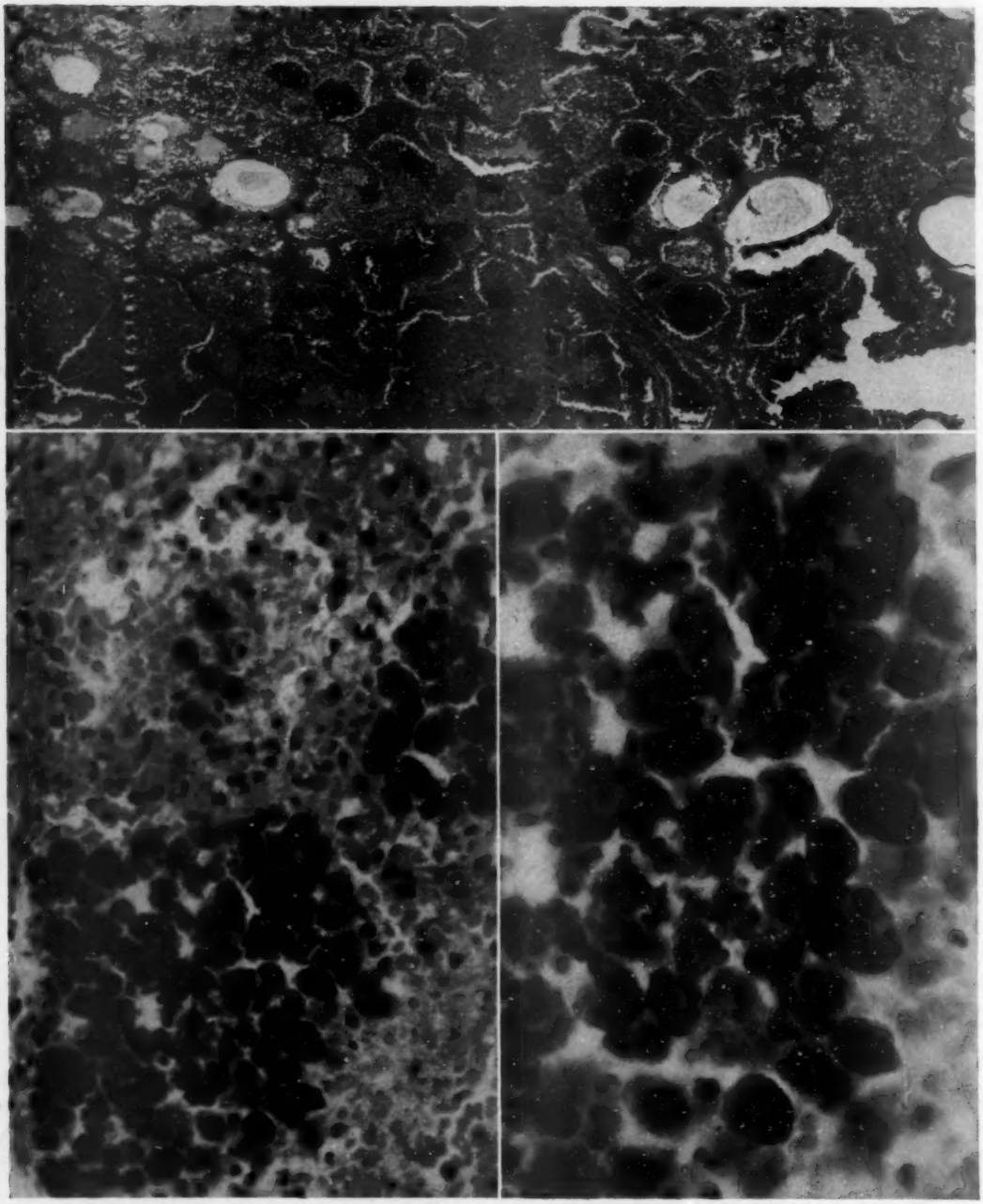

Fig. 4. Case II. D. D. Histopathologic details of lung showing siderofibrosis. Irregular clumps of macrophages containing hemosiderin, mostly intra-alveolar. Thickened septa and severe chronic passive congestion. (Hemotoxylin and eosin, 35×, 400×, 950×.)

January, 1935, to December, 1947. Mitral stenosis and regurgitation without congestive signs were recorded in 1944. At that time we did an intracutaneous tuberculin test with 0.0001 mg. P.P.D. and found it positive at thirty-three and forty-eight hours. He has never been exposed to dust hazards. At the present he continues working, but has periodic dyspnea and slight weakness. This is interpreted as arising from his heart damage. Our

first diagnostic inquiry was directed toward rheumatic pneumonia, a much debated entity. However, we could find no basis in the literature or from consultation with Drs. Thomas McMillan and Charles Wolferth to warrant the conclusion that the nodulations were due to rheumatic pneumonia.

The roentgenograms (Fig. 1 and 2) reveal a nodular lesion, generalized in both lungs, observed from 1935 to 1947. On January 8, 1935, there was a bilateral pneumonia and a background of definite nodulation (portable machine, supine exposures). The next study shown was of July, 1935, when the pneumonia had cleared. It is not certain that the nodules have changed. On June 17, 1941, the nodules seem larger, but the roentgenogram is very high in contrast. The heart may be larger. On May 9, 1944, we see that there is confirmation of larger nodules, which are definitely more distinct than in 1935. The heart appears unchanged. In December, 1947, there is no change in the nodular character (since 1941), but the heart seems larger. In all studies the characteristic mitral configuration was apparent by both postero-anterior and lateral exposures. The patient is living.

Following this, 3 cases of rheumatic mitral disease that bore great similarity to Case 1 were found at the Philadelphia General Hospital. On these, Dr. William Ehrich very kindly uncovered what lung tissue had been saved and described for us the histopathologic details. Dr. Ehrich warns that the specimens studied are so small (since interest in this disease was not active at the time of necropsy) that they may not be representative of the entire lung. However, the histopathologic and roentgenologic character coincide strikingly with material found in the literature.

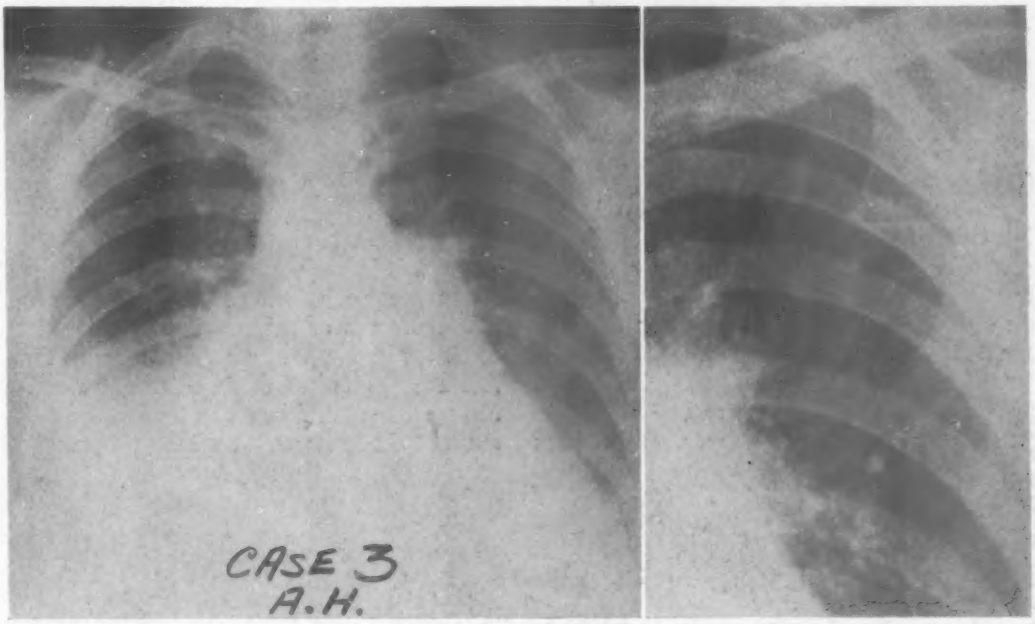

Fig. 5. Case III. A. H. Patient dying of rheumatic mitral disease with autopsy diagnosis of pulmonary hemosiderosis. The roentgen nodules measure up to 2.5 mm. and are seen easily on the original.

Case II. D. D. (Fig. 3 and 4), male, white, aged fifty-eight. Rheumatic fever at the age of four. Shortly before final hospitalization he suffered recurrent ankle edema. Death occurred in decompensation.

The roentgenogram (Fig. 3) demonstrates marked nodulation, generalized, the nodules measuring up to 3 mm. in diameter. The heart indicates a double mitral lesion with marked ventricular hypertrophy.

Autopsy showed mitral and aortic stenosis

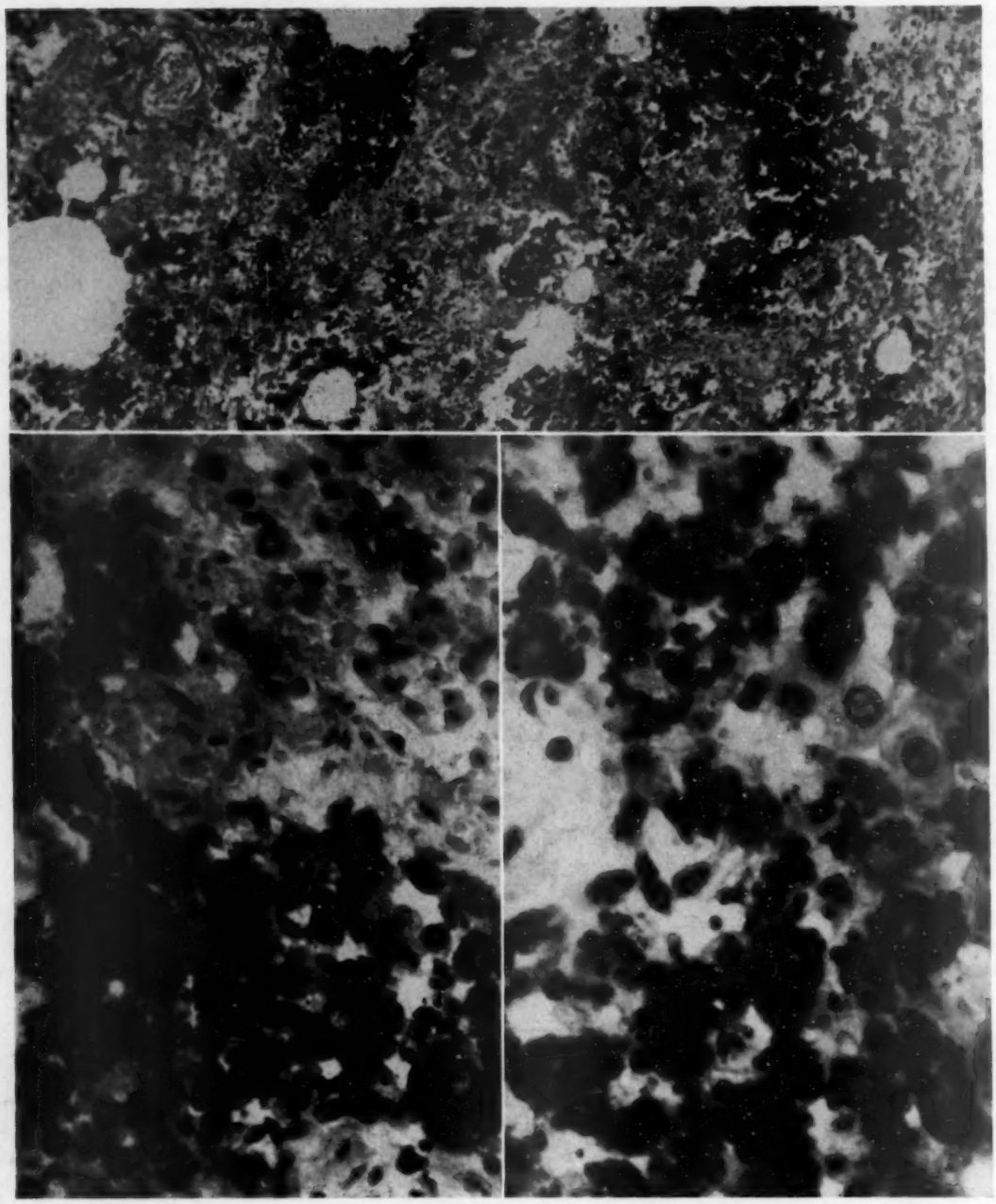

Fig. 6. Case III. A. H. Histopathologic details of lung showing hemosiderosis. Macrophages containing the pigment are intra-alveolar and interstitial. Nodules are 2 to 3 mm. in diameter but are of irregular outline. Hematoxylin and eosin with Prussian blue counter-stain, confirming the presence of iron. 100×, 400×, 950×.

and insufficiency (rheumatic) and myocardial hypertrophy. Histopathologic study of the lung reveals siderofibrosis. The slide contains hemosiderin collections large enough to be seen easily by the naked eye. Dr. Ehrich's description follows: Microscopic examination of the only piece of lung available reveals the picture of marked chronic passive congestion with siderofibrosis (Gamna-Gandy bodies). The capillaries are engorged with erythrocytes. The alveoli

contain numerous erythrocytes and some polymorphonuclear leukocytes. A portion of the alveoli is packed with macrophages containing large quantities of a yellow pigment, obviously hemosiderin. Some of the septa of the alveoli are thickened; the fibers composing the septa are rather straight in part and obviously incrusted with calcium. In other areas one finds round calcium clots as well as segmented yellow rods; the latter are mostly engulfed by foreign body giant cells. The pleura and the interstitial tissue show a good deal of coal pigment. There

Autopsy: Rheumatic mitral valvulitis, aortic and tricuspid valvulitis, dilatation of the left ventricle and hypertrophy of the right ventricle. Dr. Ehrich's description follows: Microscopic examination of the lungs reveals marked thickening of the septa, which are infiltrated with macrophages containing abundant blood pigment. The alveoli contain numerous densely crowded macrophages, mostly with much blood pigment, as well as proliferating bronchial epithelial cells, occasionally with mitotic figures. These various changes are definitely focal

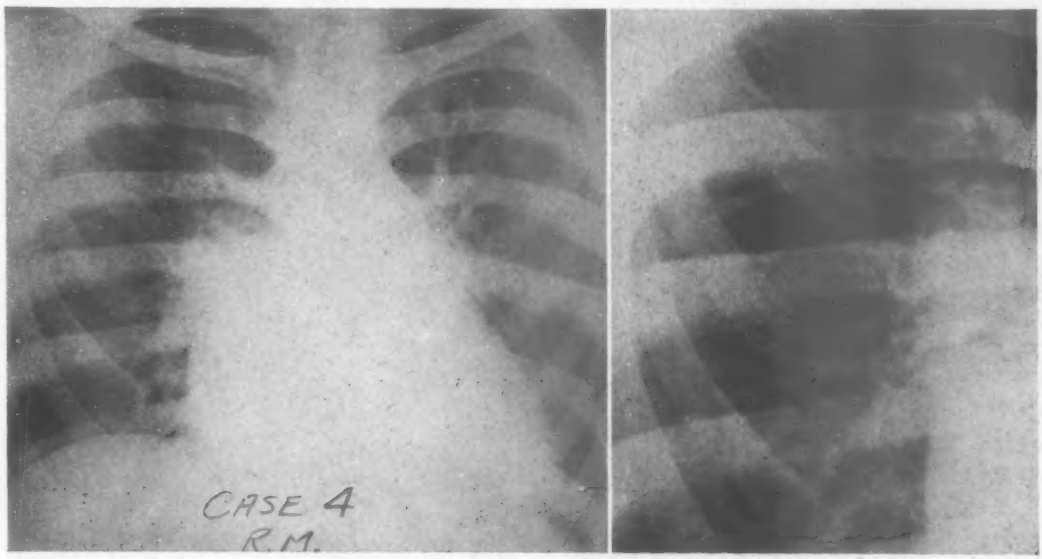

Fig. 7. Case iv. R. M. Patient dying of rheumatic mitral disease with autopsy diagnosis of pulmonary siderofibrosis. The nodules cannot be seen on the reproduction but measure up to 1.5 mm. on the original. Poor aggregation of iron is shown on the histopathologic slide.

are nodules measuring 1 cm. in diameter that are loaded with this pigment. Nothing suggests silicosis or asbestosis.

Case iii. A. H. (Fig. 5 and 6), female, white, aged thirty-five. No history of rheumatic fever. For six years there were increasing shortness of breath, fatigue and weight loss and more recently swelling of the legs and palpitation. On hospital admission there were bubbling and moist rales, a precordial bulge and thrill, a systolic mitral murmur and a presystolic slur. Electrocardiogram showed right axis deviation and inverted T waves. There was no response to digitalis and penicillin.

The roentgenogram (Fig. 5) reveals obvious small densities up to 2.5 mm. in diameter and a heart suggesting a double mitral lesion.

in character, causing poorly outlined nodules measuring 2 to 3 mm. in diameter. The pleura of the lung is thickened in some places and covered with a layer of fibrin. There is some infiltration with lymphocytes. The diagnosis is severe chronic passive congestion, fibrinous pleuritis and hemosiderosis (but no siderofibrosis).

Case iv. R. M. (Fig. 7 and 8), male, white, aged twenty-four. The clinical history is not pertinent. The clinical diagnosis at death was rheumatic heart disease with auricular fibrillation and perhaps bacterial endocarditis; and epilepsy.

The only roentgenogram available (Fig. 7) shows very fine stippling in the upper two-thirds of the lungs, easily overlooked. The

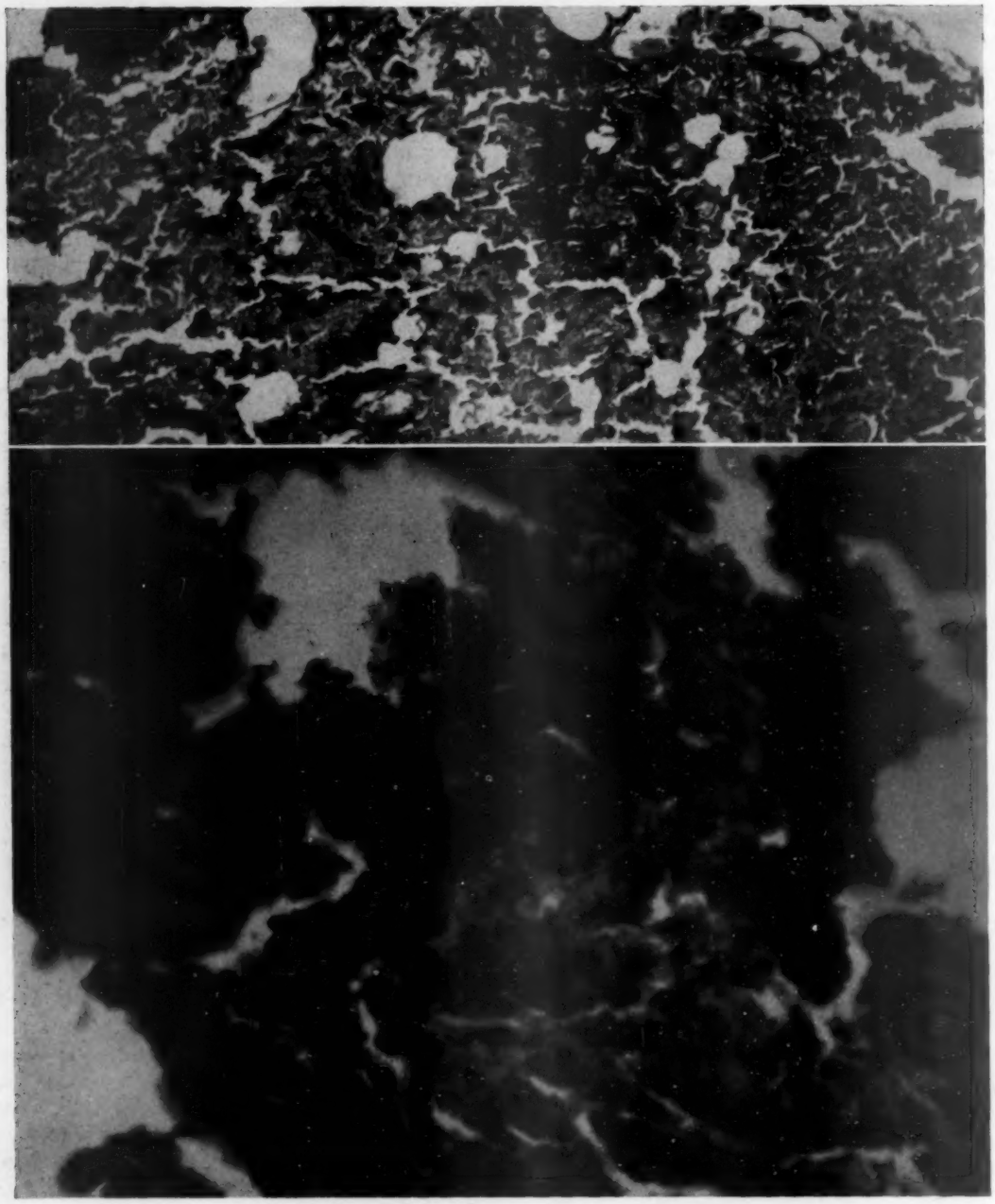

Fig. 8. Case IV. R. M. Histopathologic details of lung showing poorly defined collections of hemosiderin-laden macrophages and chronic passive congestion. Hematoxylin and eosin with Prussian blue counterstain, confirming the presence of iron. 100×, 950×.

largest nodules measure 1.5 mm. and are very faint. The clumps of macrophages together with hemosiderin and fibrosis are hardly large and dense enough to cause roentgen nodules. The hemosiderin can be seen by the unaided eye on the tissue slide, but it is not well aggregated. The heart contour suggests a double mitral lesion, enlarged ventricles and a large pulmonary artery.

Autopsy: Dilatation and hypertrophy of both

ventricles and healed rheumatic mitral valvulitis. Dr. Ehrich's findings were as follows: The capillaries are engorged with erythrocytes. The alveoli are partly collapsed, while many are crowded with large numbers of macrophages filled with a yellow pigment, obviously hemosiderin. In the parenchyma of the lung as well as under the pleura one finds areas measuring 1 mm. in diameter where the macrophages are particularly numerous. Here the connective tissue reveals fibrosis and there are calcium incrustations of some of the fibers, as well as a few segmented yellow rods. There is nothing to suggest silicosis or asbestosis. The various sections of the lung available reveal the characteristic picture of chronic passive congestion with multiple areas of siderofibrosis.

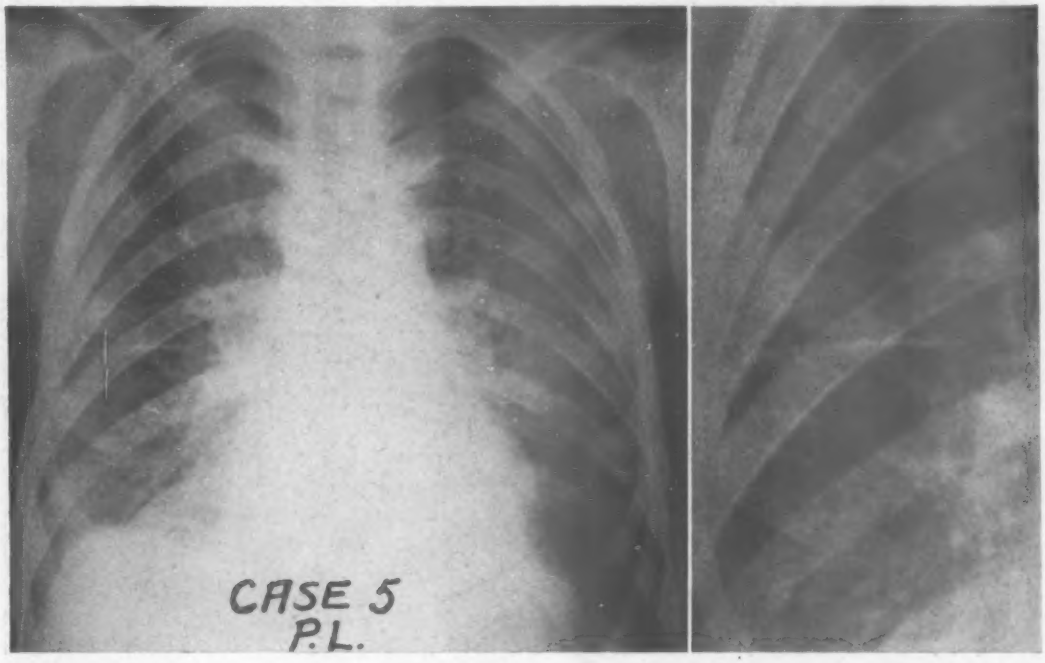

Fig. 9. Case v. P. L. (Case courtesy of Dr. Merrill C. Sosman.) Patient dying of rheumatic mitral disease with autopsy diagnosis of pulmonary hemosiderosis. Diffuse nodulation well seen on the original, but most of nodules are not over 1.5 mm. in diameter and not very dense.

Case v. P. L. (Fig. 9 and 10), male, aged twenty-four. (Generously provided by Dr. Merrill C. Sosman of Boston.) The patient had rheumatic fever at the age of four and was incapacitated by his heart from 1933 to 1934, when he was hospitalized with dyspnea and cyanosis. There were heart murmurs of aortic and mitral stenosis and insufficiency. Thoracentesis on the right repeatedly secured large amounts of fluid. Death occurred on the twenty-second hospital day.

Roentgenograms show a generalized fine nodulation in the lungs, together with moderate engorgement of vessels and a small amount of pleural effusion. The nodules are not over 1.5 mm. in diameter for the most part, but occasionally reach the size of 2 or 3 mm. On the tissue section they measure 1 mm., the discrepancy probably being due to multiple superimposition in the roentgenograms. The heart indicates enlargement of the pulmonary artery and the right ventricle.

Autopsy: Cardiac enlargement, adherent pericardium, stenosis of tricuspid, mitral and aortic valves and fibrinous vegetations on the free margins of aortic and mitral valves. The histopathologic lung findings as described by Dr. Ehrich are as follows: Edema and engorgement has created a thickening of alveolar walls, in some of which there is an inflammatory reaction consisting of fibroblast growth and infiltration by mononuclear and lymphoid cells.

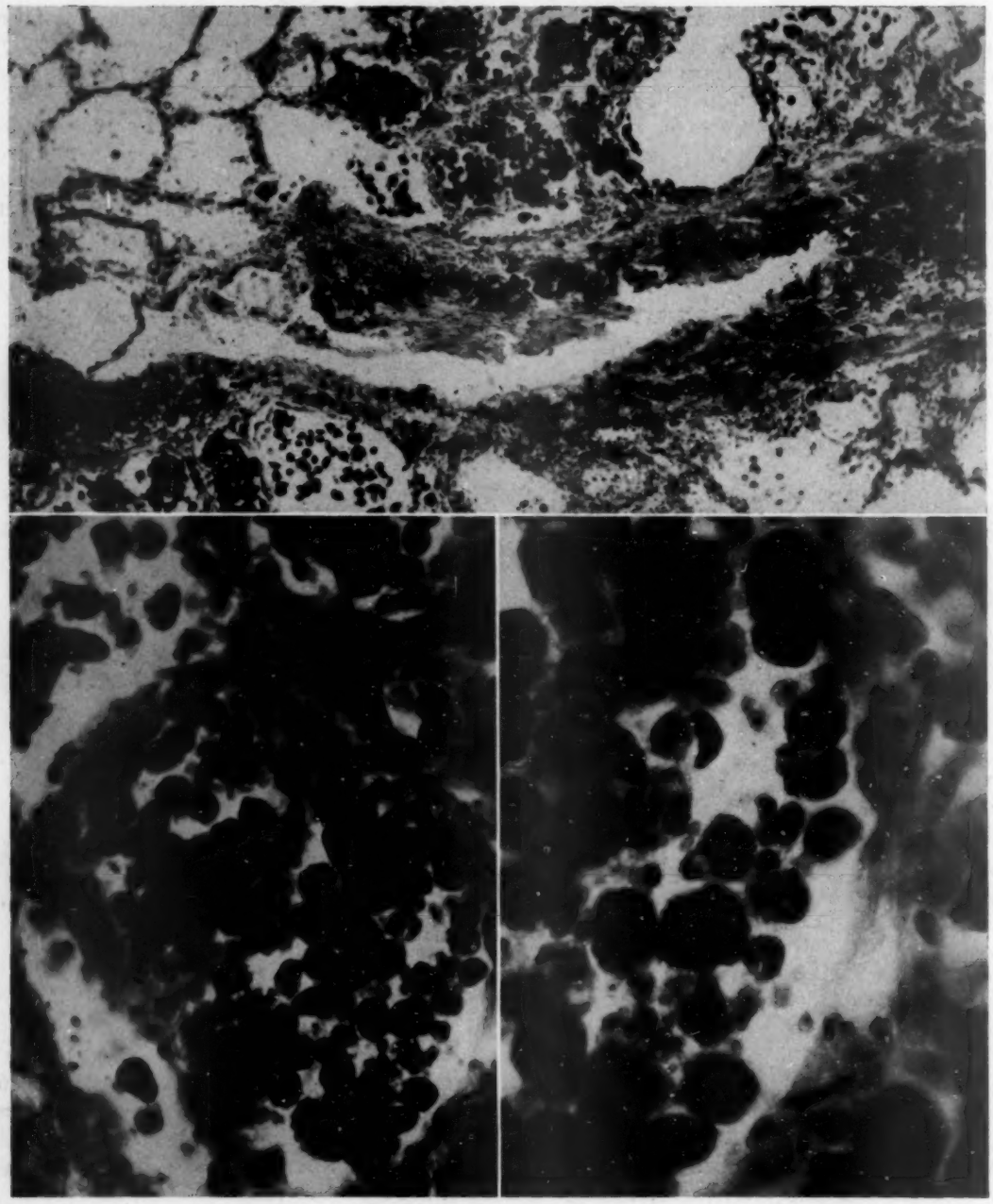

Fig. 10. Case v. P. L. (Case courtesy of Dr. Merrill C. Sosman). Histopathologic details of lung demonstrating chiefly alveolar but also interstitial location of hemosiderin-laden macrophages. The foci of iron-laden alveoli measure about 1 mm. in diameter. Hematoxylin and eosin with Prussian blue counter-stain, confirming the presence of iron. 100×, 400×, 950×.

There is intra-alveolar deposit of fibrin and leukocytes with transition to completely organized plugs. There are foci of alveoli, measuring about 1 mm. in diameter, that are filled with hemosiderin-laden macrophages. Histopathologic diagnosis: Chronic passive congestion with marked hemosiderosis and so-called rheumatic pneumonitis.

Case vi. E. R. (Fig. 11), male, white, aged thirty-two. (Referred by Dr. J. Warren Hundley of Philadelphia.) The patient had rheumatic fever and diphtheria at the age of six. He felt well until 1944, when he noted shortness of breath, progressively increasing. Bed rest was necessary in August and October, 1947, for cough, fever and fatigue. There were recent night sweats, blood-streaked sputum and a characteristic rheumatic cardiac contour (including moderate left atrial enlargement), encouraged us in making this diagnosis after our acquaintance with the preceding 5 cases.

The patient was discharged to rest at home for six weeks prior to resuming light work. Follow-up visit one year later revealed no change in the pulmonary lesion, but an increased heart size and continued fatigue.

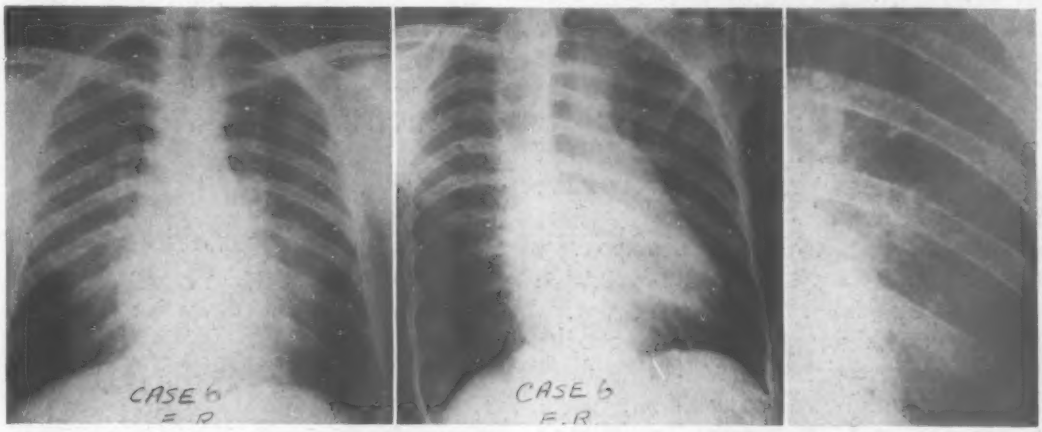

Fig. 11. Case vi. E. R. Patient living and working with mitral stenosis and insufficiency. Roentgen study elsewhere indicated miliary tuberculosis, but tuberculin skin tests and sputum negative repeatedly. No change in the roentgenograms taken over a period of four months. A generalized nodular lesion just like that in the other cases is seen in all of this patient's studies.

fever of 102° F., which dropped abruptly under penicillin. No known exposure to tuberculosis exists. A chest roentgenogram elsewhere was diagnosed as miliary tuberculosis. He was admitted in December, 1947, with the following findings: Normal cardiac rhythm; a marked thrill at sixth interspace, palpable at both lung bases; a presystolic crescendo and faint systolic murmur at the apex and a short soft systolic murmur at the pulmonic area. There were wheezes in the upper lung areas and fine crepitant rales in the posterior and lateral bases. Old tuberculin skin tests were negative to 0.1 cc. of 1:100,000 and 0.1 cc. of 1:1,000. Three sputa and two gastric washings were negative for acid-fast bacilli. The temperature was normal and the blood culture negative. Clinical diagnosis: Rheumatic heart disease; mitral stenosis and insufficiency; cardiac enlargement.

Roentgen diagnosis on admission: Pulmonary hemosiderosis, secondary to rheumatic mitral disease. The generalized nodulation evenly distributed throughout both lungs, coupled with a

Discussion

The 4 autopsied cases all show chronic passive congestion, some of which is severe. Two cases reveal hemosiderosis and two siderofibrosis. All histopathologic slides carry nodular aggregates that are visible by the naked eye and can be identified as areas of hemosiderin deposition. Three of the tissues have been stained with Prussian blue to confirm the diagnosis. The aggregates of iron pigment vary in size from 1 to 3 mm. in diameter. Apparently, not only the size but also the distribution and shape of the nodules governs the degree of roentgen visualization.

Thus, from the roentgen and microscopic study by other authors and ourselves it seems that *focal clumps* of hemosiderin and macrophages, with or without fibrosis and calcium deposition, can cause densities large enough to be seen on roentgenograms

of the lungs. This phenomenon occurs rarely in severe chronic passive congestion, in those dying of rheumatic mitral disease. It also occurs in mitral disease patients living comfortably without clinical evidence of congestion of the lungs. These persons may be supposed to be supporting a hemosiderosis with *inactive chronic passive congestion* (a phrase permitted by our colleagues in pathology). This is demonstrated by our 2 living cases and by the several living cases from New York[12] (although a different interpretation was placed on the latter by the reporting authors).

The presence of conglomerations of iron pigment makes these cases most interesting for comparison with the several groups, mentioned above, which have a similar, finely divided lung lesion, demonstrable roentgenographically. The cases of this report belong to the group of endogenous hemosiderosis, which includes the fatal anemias of children. The welders, rouge workers and metal grinders demonstrate the exogenous siderosis. Hemosiderosis of itself, as is true of pure siderosis, is a benign lesion, without attendant disability.

Carrying the roentgen diagnosis further, our cases would be problems to differentiate from the common pneumoconioses or miliary tuberculosis. The tell-tale evidence consists of the mitral configuration of the heart and the history of rheumatic valvular disease. A host of other diseases may and have been the subject of differential consideration. The following list is revealing:

Miliary tuberculosis	Bronchiolitis obliterans
Pneumoconiosis	Chronic passive congestion
Periarteritis	Polycythemia
Sarcoidosis	Brucellosis
Metastatic carcinoma	Tularemia
Histoplasmosis	Psittacosis
Ascaris infestation (?)	Leukemia
Aspergillosis	Hodgkin's disease
Bilharziasis	Lupus erythematosis
Bronchopneumonia	Xanthomatosis

SUMMARY

To the limited literature on pulmonary hemosiderosis due to mitral heart disease, we have added a report of four autopsied cases, and two living cases observed for several months and thirteen years respectively. In our findings there is confirmed the work of earlier (chiefly European) authors to the effect that this disease very rarely causes a deposition of hemosiderin in lung macrophages in sufficiently large clumps (1 to 3 mm. in diameter) to be recorded as a finely nodular roentgen density. This lesion must be differentiated from a host of diseases. A comparison is drawn between cases of endogenous hemosiderosis, exogenous siderosis due to iron dust, silicosis and miliary tuberculosis.

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DISCUSSION

Dr. George V. LeRoy, Chicago, Ill. I found this report very interesting indeed, and would like to congratulate the authors on calling to our attention yet another curious manifestation of rheumatic mitral disease. At the present time when mass roentgenography is gradually achieving its goal of an examination of the entire population it is well to appreciate the fact that a multiplicity of processes may yield a coarse nodulation throughout the lung fields. Most internists when confronted with films like the ones shown here would, I believe, be inclined to assume that their patient's rheumatic heart disease was complicated by some one of the serious conditions that Dr. Lame has cited in his list of differential diagnoses. Many of us, I am sure, would undertake as rigorous and complete a diagnostic study as possible, and even in the face of negative findings would be likely to take a fairly serious view of the roentgen findings. Recently, we had an elderly pa-

tient with congestive heart failure due to arteriosclerotic heart disease whose roentgenograms were similar to those we have seen today. He was examined repeatedly by several chest specialists, was bronchoscoped at least twice, underwent repeated gastric lavages and innumerable skin and sputum tests. At autopsy the lungs displayed chronic passive congestion and brown induration. It will be interesting to get the sections to determine whether hemosiderosis of the sort described was also present.

The importance of this report to clinicians consists, I believe, in the fact that the condition that is described is relatively benign when compared with most of the other causes of similar roentgen changes in the chest roentgenogram. The long duration of these findings in the first case—thirteen years—is evidence of this. The other clinical reports are too incomplete to permit an evaluation of this element; but I find it easy to believe that the lesions are harmless. Patients who display this sort of lesion must have some peculiar type of tissue reaction to the hemoglobin phagocyted in their alveoli, for it is certainly true that the majority of patients with rheumatic mitral disease have hemoptysis at one time or another, and most of them do not develop lesions of this sort.

I think it is not completely proper to group hemosiderosis and siderofibrosis with the so-called exogenous sideroses. The common feature of these three states is the presence of iron in the reacting tissue. In the forms of pneumoconiosis due to iron-laden dusts the size of the particles is probably critical. It is also of importance that the iron is in a metallic state, or in the form of an insoluble salt, as the oxide. The iron in hemosiderin forms a very small part of the molecule—less than 1 per cent—and under healthy conditions may be split off and returned to the body's iron pool. Likewise, with any deposit of hemosiderin there may be other iron-free residues of hemoglobin which have the same golden appearance in sections. The occurrence of calcification and ossification in the alveoli of patients with chronic congestive failure has been mentioned by many writers; and one is entitled to wonder how much of the shadows we see in these cases may be due to this phenomenon rather than to a reaction to the iron. The ease of the Prussian blue test may be misleading; and just because iron is present in such nodules is not adequate proof that iron caused them, in the sense that iron causes lesions in lungs of arc welders, for example.

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THE APICAL FORM OF BRONCHOPULMONARY CANCER

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THIS is the most characteristic clinical form of bronchopulmonary cancer. Its primary development in the apex of the lung and, later, extension to the thoracic dome, is what gives it its nosological individuality and denomination as "cancer of the thoracopulmonary apex."

The site and growth of the tumor is characteristic, as this occurs in a region that forms part of the entrance to the thorax and is therefore crossed by important nerve elements whose alterations become exteriorized by typical symptoms, that, on being grouped together, constitute well known syndromes. The order of appearance of the symptoms is governed by the progressive development of the thoracopulmonary blastoma.

Though we say "bronchopulmonary," it should really be "bronchial," as our personal experience has proved it to be of bronchial origin, and not *branchial* or embryonal, as held by Pancoast when he speaks of them as "tumors of the sulcus pulmonaris superior." Neither have we been successful in encountering the metastatic forms due to neoplastic processes of other viscera, referred to by other authors.

After eighteen years of study of this clinical form of bronchopulmonary cancer, it is of special interest to note the regularity of the symptomatology and its appearance in definite stages, so that the development may be followed accurately to the end, as long as the evolution of the disease is not interrupted by death due to some intercurrent process.

The character of the symptoms and evolution of the localized neoplastic process in the thoracopulmonary apex amply justifies the opinion of the great Uruguayan physician, Dr. Ricaldoni, when he stated in 1918, "that there are more than enough reasons to group these lesions under a separate heading and that, in view of their mode of constitution, they should be called *irradiating lesions of the pleural dome.*" His masterly description of the symptoms that form this syndrome and his precise conception of the individuality of this pathological process have led us to give his name to this clinical form of cancer of the thoracopulmonary apex.

By so doing we are not overlooking Hare's important contribution when, in 1838, he described a patient who was suffering from "pains, prickliness and numbness along the ulnar nerve of the left arm, which were more pronounced in the elbow, where there was slight oedema and redness. There was also pain in his left scapula, but showed no physical signs on examination of the lung." The only possible source of this was a tumor found in the triangle on the left side of the neck, that according to Hare, "possibly compressed the origin of the branches of the brachial plexus."

Besides, Hare's patient also had left ocular signs, such as myosis and paralysis of the levator palpebrae superioris; these are mentioned in the case history, but with no comments.

His case, therefore, presented both the radicular and sympathetic symptoms and the tumor situated in the thoracic apex, but perhaps due to insufficient means of exploration, lacked the pulmonary apex symptoms.

However, it is impossible to speak of cancer of the thoracopulmonary apex without referring to the great American clinician and radiologist, Pancoast, and to his important contributions and the fundamental principles he laid down; these should be known to every practitioner, inasmuch as they enable us to reach a rapid diagnostic identification of the clinical form of this neoplastic process.

The important investigations carried out in Argentina, North America and Uruguay have brought this condition before the attention of the medical profession, while other American countries have also added valuable contributions; this has undoubtedly helped to stress the clinical and pathological individuality of this process, the knowledge of which is almost entirely due to the efforts of the medical science of our continent.

In a synoptic chart we have summarized the clinical evolution and main symptoms of this disease, and the syndromes that have been described up to the present.

We divide the evolution of cancer of the thoracopulmonary apex into four periods, as follows:

1st stage—onset
2nd stage—of extrapulmonary invasion
3rd stage—of characterization
4th stage—last period.

1. The *initial* period corresponds to the moment when the neoplastic lesion begins in the pulmonary apex and there are no physical nor functional symptoms, or if any, they pass unnoticed or they are attributed to another cause. A roentgenogram taken during this period shows a faint shadow in the apex of the lung; however, this very appearance is also found in cases of apical pleuritis, so we are deprived not only of the possibility of establishing an early diagnosis, but also of all the therapeutic advantages derived from it.

Perhaps bronchoscopy may, at some future date, enable us to discover the tumor in its intracanalicular initiation. Transthoracic puncture may also be attempted as a means of providing biopsy material.

2. *Extrapulmonary Invasion.* In its development the neoplastic lesion invades—either directly or by metastatic lymphangitis—the internal aspect of the greater supraclavicular fossa; that is to say, what is known as the thoracic apex; thus a single tumor mass is formed: that of the thoracic apex with that of the pulmonary apex. This tumor compresses all the structures lodged in the supra-retropleural fossa and its neighborhood; in other words, it affects the roots of the eighth cervical and first dorsal nerves and, at times, the stellate ganglion.

The compression of these nerve roots and their neoplastic infiltration brings about a radiculitis of the inferior brachial plexus, which is clinically shown externalized by pains of dull onset, that later become unbearable and resistant to all treatment.

It is at this stage that the patients begin a disheartening tour of hospitals, where they are usually treated for arthritis and many roentgenograms of the shoulder are taken, the results of which are negative, as can be expected. Others are considered cases of rheumatic neuritis and undergo all sorts of treatments, among which diathermy, short-wave therapy and ionophoresis are not omitted.

A knowledge that a radiculitis can be the result of an apical cancer should lead to a roentgenogram of the thorax in the presence of pain in the shoulder and the inner aspect of the arm. It is to Pancoast that we owe this important step that guides us to a correct diagnosis, inasmuch as on finding an apical shadow in the lung of a patient suffering from inferior brachial radiculitis and, much more so if there is already a shadow in the thoracic apex, it can be established that the cause is a cancer of the thoracopulmonary apex.

Having found the two clinical elements which constitute the *thoracic syndrome* of Castex, Palacio and Massei—viz., inferior brachial radiculitis and a roentgenographic thoracopulmonary shadow—it is possible to establish a fairly early diagnosis of cancer of the thoracopulmonary apex.

The speed with which blastoma invades the sympathetic fibers is manifested by the early or late appearance of oculopupillary and facial vasomotor symptoms, that may become evident during this period or appear in the following one.

3. *The Characterization Period.* It is during this stage that all the signs and symptoms appear which characterize this clinical picture.

They are, in order of appearance: (1) The *roentgen shadow of the apex.* (2) *Radicular pains of the inferior brachial plexus*, accompanied by hypotrophy or atrophy of the muscles receiving their nerve supply from the eighth cervical and first dorsal; besides, there is a slight, but evident reduction of their active movements. Inferior brachial paralysis which, associated with (3) the *sympathetic paralysis*, that is either limited to the ocular globe or affects also the communicant-rami 2, 3, etc.—established by redness and perspiration of the right side of the face—constitute *Dejerine-Klumke's* syndrome. (4) Sometimes there is a *phrenic paralysis*, which gives clinical signs of a pseudopleural effusion and roentgenologically shows a homolateral *hemidiaphragm elevation.* The phrenic symptoms may be associated with a paralysis of the recurrent nerve, especially when the blastoma is situated in the left side; in this case there may be present anginoid disorders that, associated with the earlier symptoms, constitute *Pardal's anginous form of cancer of the thoracopulmonary apex.* (5) At a certain stage of the disease, the study of serial roentgenograms reveals signs of *osteolysis*, which is a typical sign of the malignancy of the process. They also show how the apical shadow can either remain within its former boundaries or has invaded neighboring zones, thus becoming pseudolobar or lobar, according to whether it occupies part or the whole of the upper lobe of the lung. (6) The extrapulmonary progress of the process is shown clinically and roentgenologically by supraclavicular and supra- and infraspinous bulgings. These *bulgings*, as we termed them in our first publication on the subject in 1928, constitute the "paravertebral tumor" that, along with the nervous (radicular and sympathetic) and the apical symptoms, form part of *Tobias' painful apicocostovertebral syndrome.*

The diagnosis is easy in this third period, as all the signs and symptoms are present: a satisfactory testimony to the exactness of the diagnosis of a process that can no longer be modified, and that will shortly be confirmed by necropsy.

A further confirmation of the malignancy can be made through a biopsy of the tumor and either dyeing an extension of the material (Pavlovsky) or embedding it in paraffin, as we have done several times with our co-worker, Dr. Prado.

The disease pursues its relentless course and, before death, the patient enters the fourth and last stage.

4. The *last stage* is a result of the inward progression of the growth, which eventually reaches the spine and destroys the vertebrae. This destruction brings about a compression of the spinal cord through the meninges and a crural paraplegia, with exaggerated tendinous reflexes, Babinski's sign, hypertony, cell-albumin dissociation in the spinal fluid and sphincter disorders; moreover, there is anesthesia and trophic alterations in the zones situated below the pressure, the localization of which can be made exactly through Sicard and Forestier's method.

The ceaseless progression of the tumor is not hindered by the meningeal barrier, so eventually the cord is affected in such a manner that the spasticity of the limbs turns into flaccidity, with all the characteristics of a section of the cord.

In our first observation—published in 1928 with the pathologist, Dr. Bianchi—we pointed out the correlation between compression of the cord and cancer of the lung. In later papers we were able to confirm this from the clinical standpoint; furthermore, this assertion was afterwards supported by both Argentine and foreign sources. All this allows us to repeat here what we stated in earlier papers, that is to say, *that paraplegia through compression of the spinal cord has been seen in the last stage of all our cases of cancer of the thoraco-*

pulmonary apex, and that this occurrence is always present unless the clinical evolution of the disease is interrupted by death at an earlier stage.

From the aforesaid we may conclude *that in most cases and provided an infection does not interfere in the evolution, cancer of the thoracopulmonary apex starts as an intracanalicular process in a small bronchus and always ends with compression of the spinal cord.*

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A CASE OF CARCINOSARCOMA OF THE ESOPHAGUS*

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THERE have been a small number of tumors of the esophagus reported consisting of a commingling of two apparently different cellular components, one of them carcinomatous and the other sarcomatous. The nature and origin of these tumors is obscure and some confusion has arisen concerning their characteristics. The discovery and surgical resection of a case belonging to this group among the esophageal tumors observed at the Presbyterian Hospital, New York, has prompted us to report it and review other comparable cases appearing in the literature in an attempt to add to what little knowledge exists concerning these uncommon neoplasms.

CASE REPORT

E. R. (Unit No. 784298), a Finnish female domestic, aged forty-six, was admitted to the Presbyterian Hospital in August, 1945, at which time her complaints were dysphagia and retrosternal pain of eight months' duration. The pain, which was at first associated only with food intake, gradually occurred spontaneously, was localized just to the left of the xiphoid and radiated into the subscapular region. Occasionally, it became severe enough to wake her. She took no medication but modified her diet to consist of semi-solid and liquid foods. The patient lost 53 pounds during this period.

Clinical Findings. Physical examination revealed a ruddy, plump female who appeared well developed and well nourished, with no grossly abnormal findings. The blood examination disclosed a hemoglobin of 11.6 grams, white blood count of 12,100, with 68 per cent polymorphonuclears, 28 per cent lymphocytes and 4 per cent eosinophiles. The plasma proteins were 7.4 grams per cent. Examination of the esophagus with barium demonstrated a polypoid filling defect in its lower third a few centimeters above the diaphragm (Fig. 1 and 2). The lesion measured about 4.0 by 5.0 cm. in diameter. The roentgenological impression was carcinoma. Esophagoscopy disclosed a polypoid tumor which was attached to the anterior wall of the lower end of the esophagus. A biopsy was obtained but proved to be inconclusive. The procedure was repeated and a more adequate biopsy was taken. The quick paraffin sections, the roentgenographic observation, and the clinical story all substantiated the diagnosis of carcinoma.

FIG. 1. August, 1945. Polypoid filling defect in lower third of the esophagus.

First Operation. In October, 1945, the lower third of the esophagus was resected through a left posterior thoracic approach. The tumor was remarkable grossly in that it could be felt to slide up and down within the esophageal lumen. The esophagus was distended by the intraluminal mass, but did not appear to be involved by the tumor and there was no evidence of metastasis. The cut end of the esophagus was anastomosed to the gastric fundus within the chest.

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Course. Her recovery was rapid and without incident. She was discharged on the nineteenth postoperative day eating normally without dysphagia.

Interval History. Two months postoperatively the patient was gaining weight, eating solid foods, and had no major complaints. Her only difficulty was a little postprandial epigastric

Fig. 2. August, 1945. Polypoid defect demonstrated in the lateral view.

fullness. Roentgen examination at this time revealed no evidence of recurrence of the neoplasm.

In March, 1947 (sixteen months postoperatively) the patient complained of anorexia and slight weight loss, but had no dysphagia or chest pain. In May, 1947, hoarseness developed. A laryngoscopic examination showed complete lack of movement on the right of the arytenoid and vocal cord, with fixation of the latter. Roentgen study in June (Fig. 3), following recurrence of dysphagia, demonstrated a left anterolateral displacement of the esophagus at the level of the first and second thoracic vertebrae. The esophagus was slightly compressed and there was no delay in the passage of the barium. A roentgenogram of the chest showed slight widening of the right paratracheal shadow. The findings at this time suggested a mass extrinsic to the esophagus. Esophagoscopy disclosed an obstruction on the right, which was considered extrinsic at a distance 27 cm. from the upper teeth. No biopsy was taken as the mucous membrane appeared normal. The clinical findings suggested metastatic disease.

Second Operation. Because the unusual nature of the tumor suggested that it would resist radiation or nitrogen mustard therapy, and because it seemed possible that a single metastasis in the upper mediastinum existed which was causing symptoms by pressure rather than by direct extension and which might be sufficiently well encapsulated to permit removal, surgery was decided upon.

In July, 1947, the right upper mediastinum was approached transpleurally. A firm tumor mass about 3 by 4 cm. in diameter was found lying between the trachea and esophagus with its upper pole wedged behind the right subclavian artery and impinging on the recurrent laryngeal nerve. It was well encapsulated everywhere except behind the artery where it continued upward along the esophagus in intimate association with it. In this region tumor was cut across in excising the mass.

Course. Hoarseness and dysphagia were relieved, though not completely eliminated, for two months. In October a mass was noted in the right supraclavicular region. Soon thereafter she complained of dyspnea and cough, and tracheal compression was suspected. Dyspnea became progressively worse. Four doses of nitrogen mustard (0.1 mg. per kg. per day) were administered with only slight relief. Stridor persisted on both inspiration and expiration. The patient died in marked respiratory distress in November, 1947.

Pathology. The preliminary biopsies made were reported as from a malignant tumor but its true nature was not recognized and it was thought to be probably an anaplastic carcinoma.

The resected segment of esophagus measured 12 cm. in length and was somewhat sausage shaped with a maximum diameter of 5.5 cm. When the tube was opened, an ovate pedunculated firm tumor was seen with a smooth

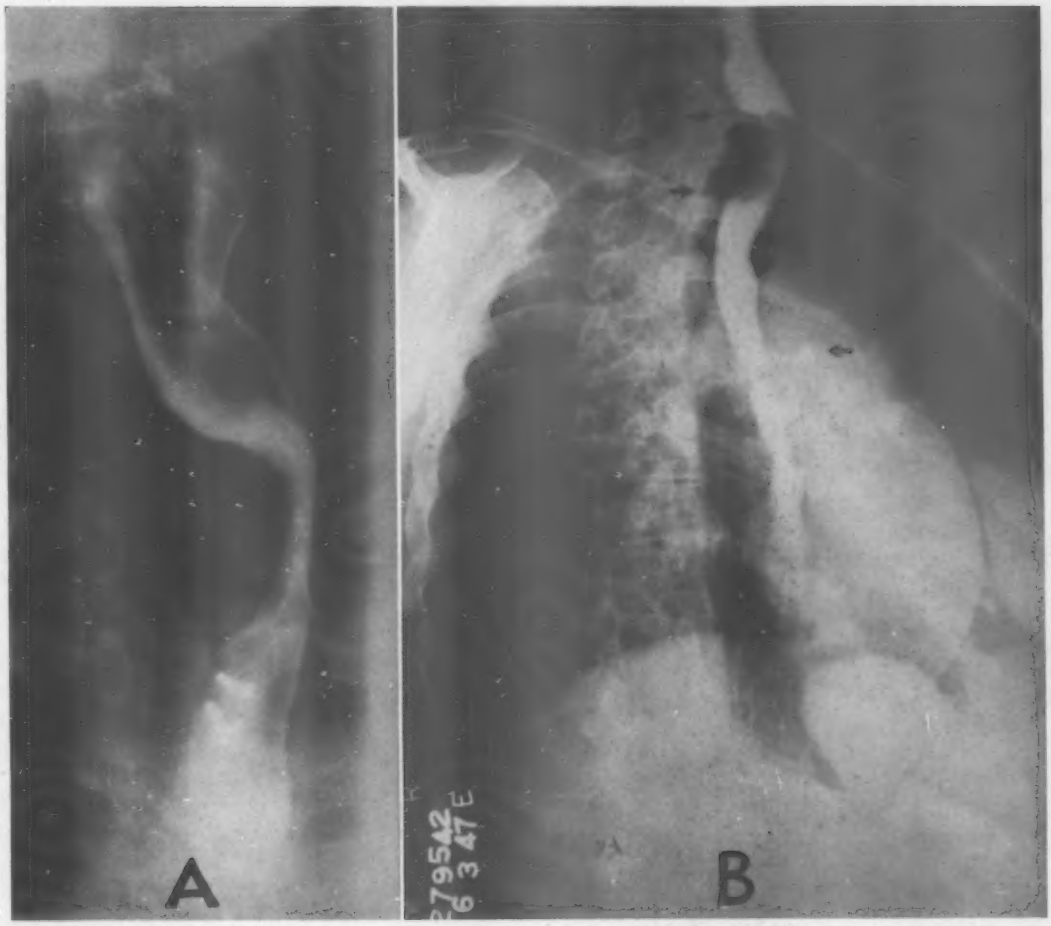

Fig. 3. June, 1947. An extrinsic mass in the right portion of the superior mediastinum displacing the esophagus anteriorly and to the left. *A*, anteroposterior spot roentgenogram of hypopharynx and upper esophagus demonstrating displacement of esophagus to the left. *B*, right anterior oblique projection. Upper arrows disclose anterior displacement of upper esophagus. Lower arrow at site of esophagogastric anastomosis.

slightly nodular surface covered with a grayish necrotic membrane. The over-all measurement was 9.5 by 5 cm. but the attachment to the wall only 6.5 by 1 cm. The cut surface of the growth was firm, pallid, and solid. It appeared to have only a superficial attachment to the esophageal wall (Fig. 4).

Microscopic examination in low power shows that the tumor has invaded the submucosa which is greatly thickened and exceedingly vascular but in no place has penetrated into the muscularis (Fig. 5). The tumor tissue is composed of two distinct elements; first, there are masses of undifferentiated epithelial cells most of which are found near the base of the neoplasm where it is attached to the esophageal wall but which occasionally can be detected also in the peripheral part, and second, the major portion of the tumor consists of a sarcomatous element which dominates the picture (Fig. 5). The epithelial cells are collected into masses outlined by a fibrous sheath. The individual cells are rounded, sometimes vacuolated, show no epidermoid differentiation nor any evidence of mucin secretion or tendency to form tubes or rosettes, and the individual cells are not infrequently separated by collagen fibers (Fig. 6). Nowhere do these cells of an epithelial habit seem to merge with the major bulk of the tumor which is made up of cells largely of spindle shape separated one from the other by a stroma rich in collagen and reticulin fibers in some places but much less so in others. These tumor cells vary enormously among

themselves from small to very large spindles and not infrequently giant forms appear which may be irregularly rounded with granular acidophilic and sometimes vacuolated cytoplasm and extremely bizarre nuclei. The general aspect of this sarcomatous portion suggests rhabdomyosarcoma although no proof of this is detected. Mitoses are very infrequent in the epithelial portions of the growth but common and often bizarre in the sarcomatous part (Fig. 6 and 7).

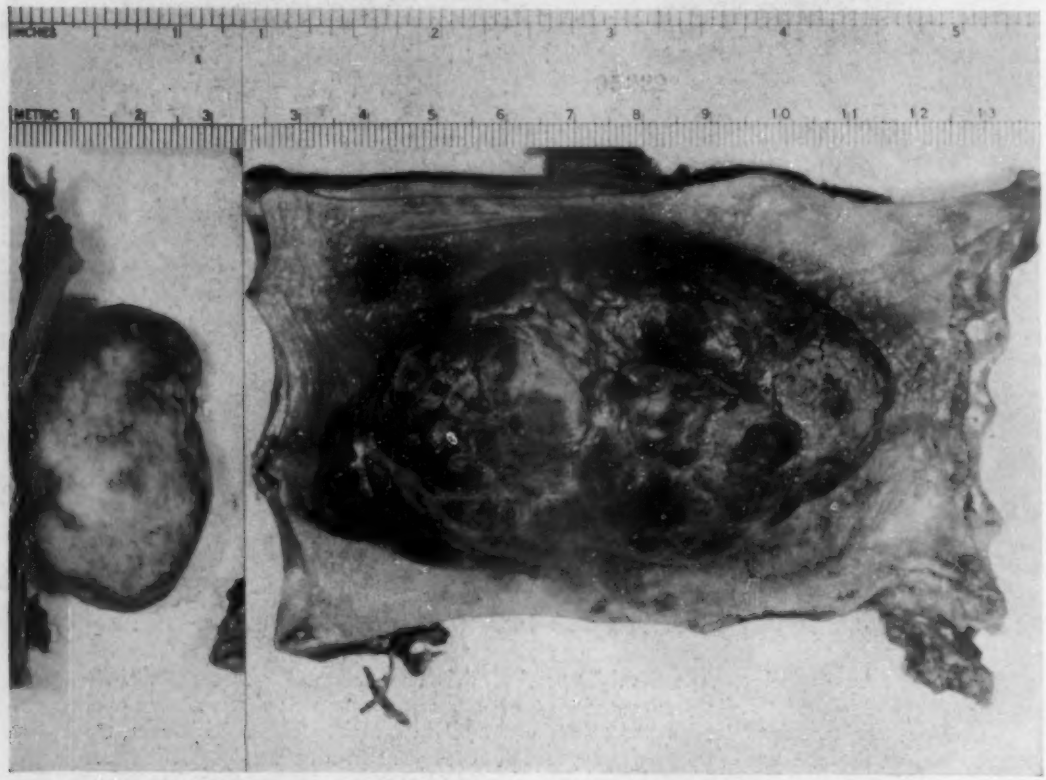

Fig. 4. Photograph of the opened esophagus showing the pedunculated tumor. At the left a cross section showing the pedicle and the absence of infiltration of the wall.

The spleen, which was removed, showed no unusual features.

The material removed at the second operation consists of small masses of tissue in which both lymph nodes and tumor tissue were recognized. Microscopically the metastatic tumor reproduces the sarcomatous elements of the primary growth. Although tumor tissue is found in close proximity to the nodes, no proof is obtained that the metastatic tumor tissue involves lymph nodes, although it is assumed that this is probably the case.

At autopsy (by Dr. Fletcher A. Miller of the Department of Pathology of the Presbyterian Hospital) a mass of tumor filled the upper mediastinum, grew into the esophagus from without, compressed the trachea and metastases were found in the superior mediastinal and right lower cervical lymph nodes but nowhere else (Fig. 8). The tumor microscopically at autopsy showed the same histopathology as was demonstrated at removal of the first metastatic mass: a reproduction of the sarcomatous elements of the tumor without any epithelial elements (Fig. 7).

COMMENT

The following are the important facts of this case. A pedunculated tumor developed on the anterior wall in the lower half of the esophagus of a forty-six year old woman, which produced a corresponding filling defect after barium was swallowed. The tumor was composed in part of a small number of undifferentiated epithelial elements, most of which were found near the base while the major portion of the growth had a sar-

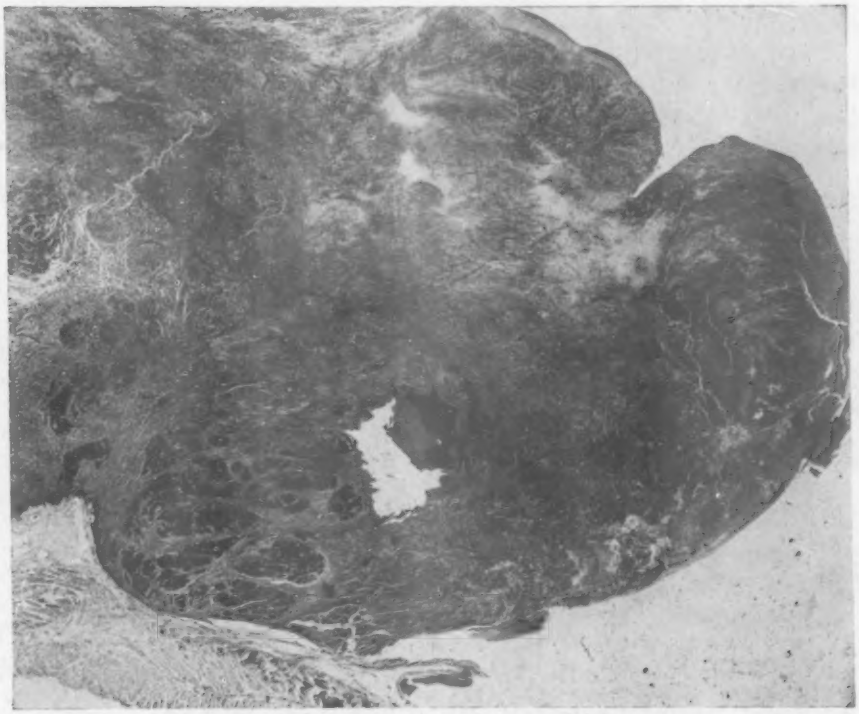

Fig. 5. Low power photomicrograph showing the failure of the tumor to infiltrate the wall. The darker areas in the tumor near its base are epithelial cells.

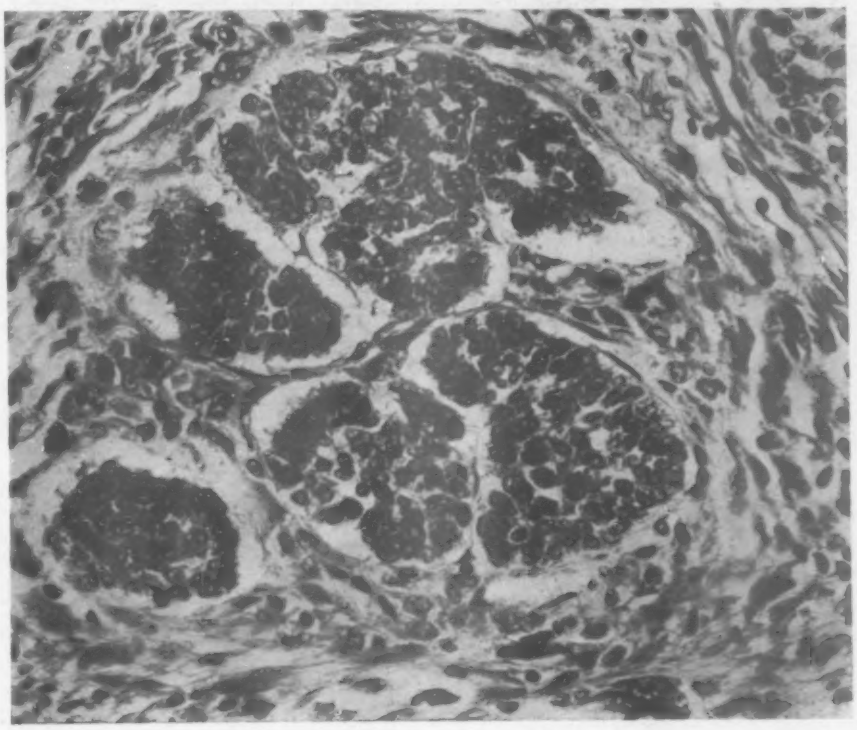

Fig. 6. Photomicrograph of groups of undifferentiated epithelial cells showing the absence of intimate relationship with the actively proliferating sarcomatous stroma.

comatous aspect suggesting rhabdomyosarcoma but without proof. Although limited to the mucosa and submucosa, it must have metastasized to the superior mediastinal nodes before its removal, although this was not appreciated at the time of operation. When these nodes enlarged an attempt to remove them failed and the persisting growth in the upper mediastinum eventually proved fatal. Except for the large recurrent mass which grew into the upper part of the esophagus, compressed the trachea and involved the right lower cervical and upper mediastinal lymph nodes, no other tumor was found at necropsy.

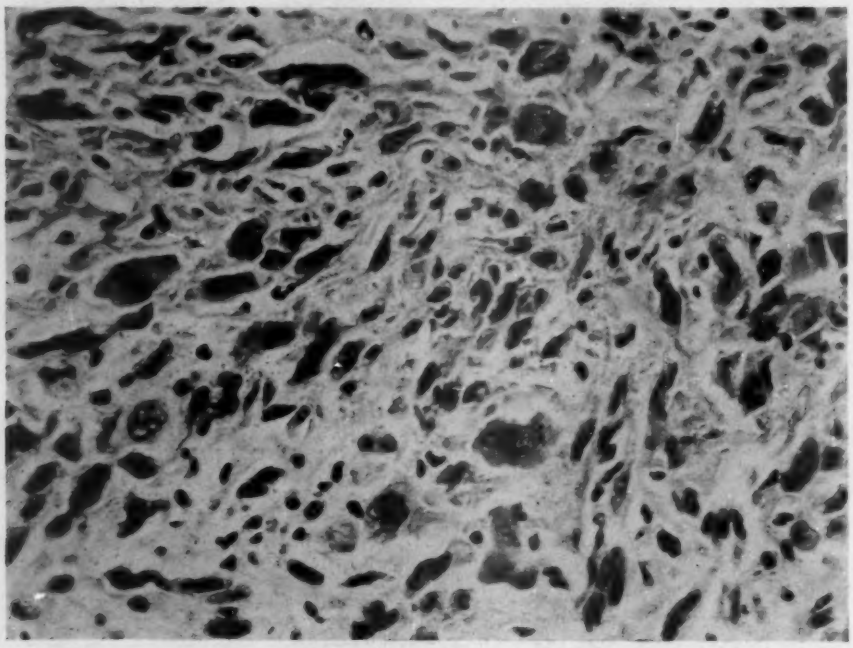

Fig. 7. Photomicrograph of metastatic tumor tissue at autopsy. The bizarre giant cells were found also in the sarcomatous part of the primary tumor.

There are reports of 10 other neoplasms which show a marked resemblance to this case. They are listed in Table 1A. They were all polypoid tumors. None was resected and all were studied at autopsy. Nine patients were males and one a female. All of the patients whose ages are recorded were forty-nine or more years of age and in every case but one the tumor was in the lower half of the esophagus. Metastases were present in 3 patients and 5 showed no metastases. In the cases of Cilotti, Heilmann, Kutsukake, Lang, Resch, and Harvey and Hamilton the epithelial tumor cells were called squamous; in the reports of Herxheimer and of Scarff this point is not clear and in Sokolow's tumor the epithelial cells were adenomatous. In all, the epithelial elements were deeply situated and the sarcomatous cells included spindle shapes and usually giant forms. The metastases of the 3 cases in which these were found consisted only of sarcomatous elements.

Ten other cases in which what are described as both epithelial and mesodermal cells were found have been included in the same table. Kinoshita's patient had a polypoid tumor in the upper esophagus at the level of the cricoid cartilage which included cartilage and myxoid elements as well as epithelial strands and sarcomatous areas. This seems to be more in the nature of a true teratoma. Cases 12 to 18 are all nonpolypoid infiltrating tumors occurring in various parts of the esophagus of elderly

men and women. In all of the cases except those of Blackburn and of Socin, the authors describe the epithelial tumor cells as squamous. In these two there were undifferentiated epithelial tumor cells. Three cases had metastases. Those from the man. None of these authors has studied personal cases and they suggest that the histopathological appearance is simply a manifestation of metaplasia occurring in squamous cell cancers of the esophagus. It is not possible, of course, to disprove this

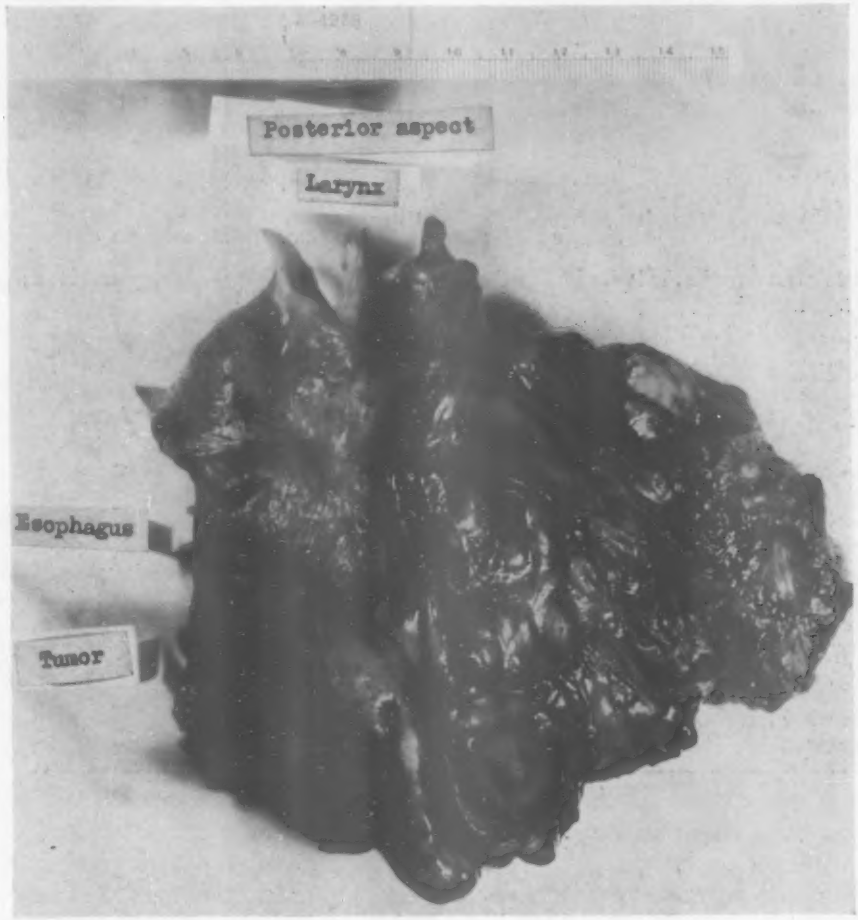

Fig. 8. Photograph showing tissues removed at autopsy. A large tumor mass projects into the opened esophagus ("tumor") and the trachea is surrounded by tumor.

tumors described by Donath and by Herzog reproduced the appearance of the primary tumor. Kahlstorf's patient showed spindle cells only in the metastases.

There seems to have been a dearth of reports of such mixed tissue tumors in recent years since the development of the operation of esophagectomy. Perhaps, because of this scarcity, doubt of the essentially dual nature of these neoplasms has been expressed by Saphir and Vass and by Pearl-hypothesis but if true it does not invalidate the observation that the tumors represented by the present one and the 10 others resembling it in Table 1A are quite different from the ordinary esophageal cancer, which is not polypoid, infiltrates the esophageal wall quite freely, metastasizes in 69 per cent of cases (Klein) and is seldom cured. Judging from the fact that only 3 of the 10 neoplasms recorded in Table 1A are known to have metastasized, one would

TABLE I

CASES OF "CARCINOSARCOMA" OF THE ESOPHAGUS

(A) *Polypoid Growths with Epithelial Elements at the Base, Sarcomatous Elements Throughout and no Epithelial Elements in the Metastases*

	Sex	Age	Size	Metastases
1. Cilotti	Male	75	Almond	Liver, pancreas, lung, pleura, 2 ribs
2. Harvey and Hamilton	Male	49	?	No mention
3. Heilmann	Male	65	14 cm. long	None
4. Herxheimer (1918)	Male	73	6 cm.	None
5. Kutsukake	Male	51	11 cm.	Regional nodes
6. Lang	Male	67	?	Liver, regional nodes
7. Lang	Male	52	Small	None
8. Resch	Male	74	10×5×5 cm.	None
9. Scarff	Male	50	1½×3½ in.	None
10. Sokolow	Female	?	8×3 cm.	No mention

All of these cases were in the lower half of the esophagus, except that of Harvey and Hamilton which was hypopharyngeal.

(B) *With Cartilaginous Elements as Well*

11. Kinoshita	Male	58	?	None

(C) *Infiltrating, Non-polyploid Growths with Epithelial and Sarcomatous Elements Diffusely Intermingled*

12. Blackburn	Female	53	Large	No mention
13. Bösenberg	Male	56	Large	No mention
14. Donath	Male	52	Large	Regional nodes
15. Herxheimer (1908)	Male	67	11 cm.	No mention
16. Herzog	Female	80	Large	Liver and regional nodes
17. Kahlstorf	Male	42	Large	Widespread, including bones
18. Socin	Female	60	Large (in diverticulum)	No mention

(D) *Cases Mentioned without Details*

19. Carnevale-Ricci
20. Hansemann

anticipate that several of these patients might have been cured had a partial esophagectomy been done.

As for the cellular origin of this tumor we have only speculations to offer. Sections of it were studied by Pierre Masson of Montreal who suggested its resemblance in some respects to the carcinosarcomas of the breasts of bitches and human females which he supposes have a common origin from epithelial elements and which differentiate in two directions both as carcinomas and sarcomas, forming what R. Meyer would call a combination tumor. In the case of this tumor Masson suggests an esophageal mucous gland as the possible source. This explanation may be correct; we have no constructive thoughts about it other than it represents an entity which differs not only grossly and microscopically but also in its biological behavior and roentgenological aspects from the usual esophageal cancer.

SUMMARY

A case of pedunculated carcinosarcoma of the esophagus is reported. The roentgen findings are illustrated in detail. After resection of the esophagus, mediastinal metastases manifested themselves. An attempt to remove all of these failed and the patient eventually died with secondary invasion of the esophagus and metastases in the mediastinum and lower cervical nodes.

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MASS ROENTGENOLOGICAL SURVEY OF THE GASTROINTESTINAL TRACT TO DETECT CANCER OF THE STOMACH

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MASS roentgenological surveys of the chest have been widely accepted as valuable methods for detecting pulmonary disease in presumably normal individuals. These surveys had wide usage in the armed forces of many countries in World War II and are now being extended to civilian life.

There are glaring defects in mass chest roentgenological examination which are commonly overlooked: first, there is the possibility of detecting more cases of pulmonary disease than there are facilities for caring for them; and second, overemphasis on the value of roentgenological methods in finding pulmonary disease at the expense of other methods of making a diagnosis, such as history, physical examination, weight charts, temperature charts, and so forth. It is indeed strange that eradication of the tuberculous food animal (as done by the veterinary inspectors of the Federal and State Bureaus of Animal Industry) is enormously successful and has diminished greatly the incidence of tuberculosis in domestic animals. These inspections have been in a sense mass surveys, but there was no resort to miniature roentgenograms.

Mass roentgenological survey to detect gastric cancer is being thought of fairly widely. Funds have been requested from both government and private sources for this type of survey. It is generally accepted that gastric cancer is the most frequent cause of cancer deaths, greatly exceeding that of any other organ or tissue. It is also widely and rightly believed that, given a sufficiently early diagnosis of gastric cancer, the outlook for cure by surgical intervention is good. Cancer of the stomach can be so insidious, however, that it is beyond any form of treatment when discovered. This is due to the absence of any symptoms or manifestations that would lead to examination of the patient either by the roentgen ray or any other means. Some great physicians and surgeons, while seemingly in perfect health, have had the diagnosis of gastric cancer made only when the disease was in a hopelessly advanced stage. One noted surgeon made the diagnosis when he felt the lump in his epigastrium while bending over the operating table! Indeed, it would be a wonderful thing if mass gastric roentgenologic surveys on well individuals could be successfully employed. It could, if found feasible, save many lives.

However, statistics on cancer and cancer deaths indicate that the high incidence of gastric cancer is exaggerated and more and more cancer of the other segments of the gastrointestinal tract and also of other regions of the body are being found more frequently. The Connecticut State figures (where cancer is reportable) for the relative occurrence of cancer of the alimentary tract are as follows per 100,000 population:

Esophagus	3.2
Stomach	15.6
Rectum	10.8
Colon	9.25
Small intestine	0.6

(1940–1946)

The only publication on mass gastric surveys to be found at the time of writing is that of Swenson.[3] He states that any great mass of people examined roentgenoscopically alone would require far more radiologists than are available for that

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purpose. Of course, using the roentgenoscopic method is a very uncertain way of detecting any early lesion. Those that would be obvious in a rapid survey with the roentgenoscope would generally be too far advanced for any sort of successful treatment; also, there would be enormous risk to the roentgenoscopist. As in mass surveys of the chest, it is the early lesion that is most likely to be overlooked by any sort of roentgen examination, and it is the early lesions for which most can be done.

At the 1947 meeting of the American Roentgen Ray Society, Kirklin and Hodgson,[1] in discussing mass gastrointestinal roentgenological surveys, demonstrated that it would be necessary to examine individuals every three months, which, for the whole adult population of the country, is an absurdity. Rigler[2] examined 544 individuals over the age of fifty, symptomless except for a low acidity or aclorhydria. He discovered by roentgen examination 3 cases of gastric carcinoma, which were found by operation. He stated that there was one case which was missed through "an error in interpretation." In his group he had 11 other cases that did have gastric carcinoma, but they were not to be considered because they were not symptomless.

To appraise critically the value of mass gastric surveys, three points will be considered:

1. The relative incidence of cancer of the alimentary tract in its several segments, as discovered by the roentgenographic method.
2. The efficiency of the opaque meal roentgen examination in detecting early cancer of the gastrointestinal tract.
3. Its numerical relationship to the number of cancers seen in a general hospital roentgen-ray department.

There are available for study of these points 30,985 examinations of the gastrointestinal tract from the years 1916 to 1947, inclusive. The method of examination, recording, and reporting was that which originated with the late Dr. Russell D. Carman and the late Dr. R. Walter Mills, and their plan has been consistently followed since with carefully annotated records.

Gastrointestinal examinations were complete in 69.6 per cent and incomplete in 30.4 per cent of the cases. A complete gastrointestinal examination consists of examining the entire tract from the esophagus downward. The oral and pharyngeal cavities and the anus are not included. The examinations were made by giving the opaque meal and watching its progress throughout the entire tract. A barium enema is included and since 1924 cholecystography has been a routine procedure. The patient is first scanned with the roentgenoscope and any findings noted. In the preliminary survey the positioning for the ensuing films, which are always made, is decided upon. The opaque meal is administered and the patient is roentgenoscoped in both the supine and erect positions, and in as many directions as seems advisable to the roentgenoscopist. As many roentgenograms are taken as are considered necessary in all cases. The function of the roentgenoscope in this material has been that of an instrument for the advantageous taking of roentgenograms. This is laborious and requires time, regardless of how expeditious and skillful the examiner may be. There are: a first examination, a five hour observation, a twenty-four hour observation, and at forty-eight hours, the opaque enema after evacuation of residual barium meal is given; on the same day, cholecystography is done. In incomplete examinations, some part of the preceding is omitted as a matter, perhaps, of economy in time or failure of the patient to return. Occasionally when the esophagus is suspect that structure only would be examined. But the effort has always been to make a complete study throughout the tract. In case of any ambiguity, any part or all of the procedure was repeated.

The roentgen diagnosis of carcinoma of the gastrointestinal tract was made in 1,352 of a total of 14,337 pathological cases.

GASTRO-INTESTINAL EXAMINATIONS--1916-1947

Gastro-intestinal Examinations - complete	69.6%)	
	)	30,985
Gastro-intestinal Examinations - incomplete	30.4%)	

CARCINOMA OF GASTRO-INTESTINAL TRACT (9.4%)

ESOPHAGUS	STOMACH	SMALL INTESTINE	COLON	RECTUM
252 (18.6%)	619 (45.8%)	3	367 (27.2%)	111 (8.2%)
	Confirmed--86%	Confirmed -- 66.6%	Confirmed--91%	Confirmed--75%

ULCERS

GASTRIC	DUODENAL	GASTRIC ULCER WITH ULCER OF DUODENUM
336	1,886	24

OTHER PATHOLOGICAL DIAGNOSES:	10,739	(34.7%)
CARCINOMA:	1,352	
ULCERS:	2,246	
	14,337	

Of the total gastro-intestinal examinations conducted during this period (30,985), it is readily seen that the percentage of pathological diagnoses (14,337) constitutes 46.3% while carcinoma constitutes 9.4% of the total of pathological cases.

Chart I

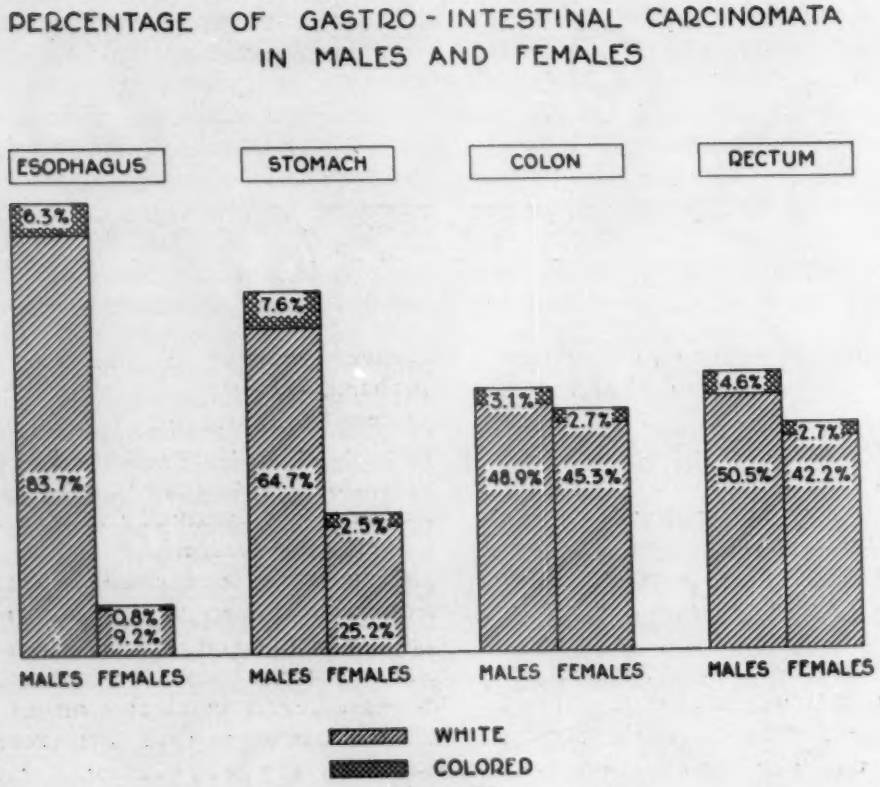

Chart II

The number of gastrointestinal examinations was 30,985, of which 46.3 per cent were of pathological import, and of these, 9.4 per cent were carcinoma.

The accompanying chart (Chart I) shows the number of cancers in the different segments of the gastrointestinal tract with the diagnoses confirmed either by autopsy, surgically, or endoscopically. The correctness of diagnosis in the case of the esophagus is unknown, but was very high. The accuracy of diagnoses elsewhere in the tract was high and shows a splendid efficiency for the roentgenographic method of examination.

In reviewing this material and considering the technique employed, it is apparent that the stomach will not lend itself to mass roentgenological surveys with any degree of success for many reasons. Among them is the time and labor required and risk involved. The fact that there is a high incidence of cancer in the other segments of the gastrointestinal tract is ignored. If all gastric cancers were diagnosed early by mass methods, there would remain a large number of cancers elsewhere in the tract that would escape detection. It must be remembered that this material was in a general hospital and practically all of the cases examined were patients with some symptoms ascribable to the alimentary tract; in other words, it is largely a pathological group; yet, the percentage of cancer is quite low. This material showed that 93 per cent of the patients studied were white. Chart II shows a relative incidence in the sexes. There is vast food for thought in the relative incidence of carcinoma of the esophagus and of the stomach in the sexes. Cancer of the colon and rectum are pretty close to the same incidence in the sexes. As to age, Chart III shows what would be anticipated—a tremendous incidence in the fifth and sixth decades.

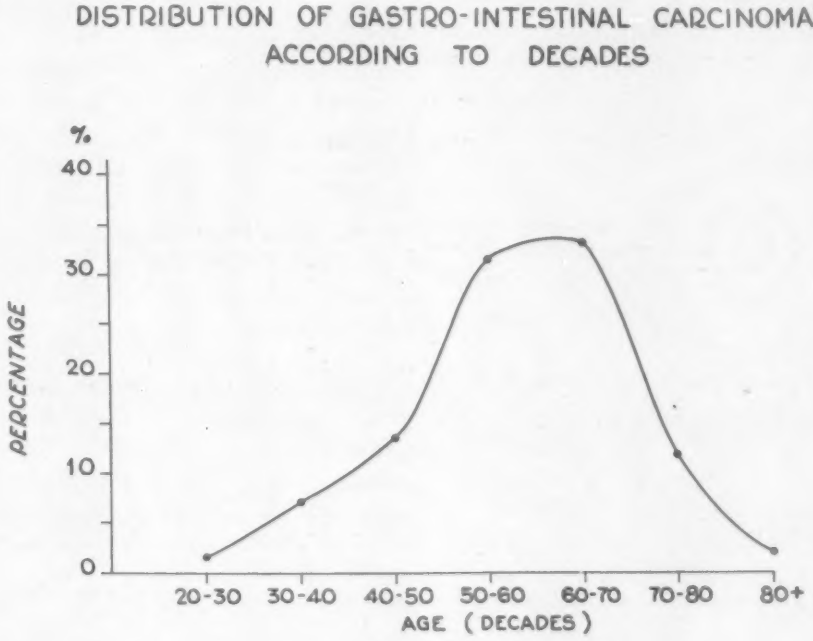

Chart III

The belief has been stated above that the frequency of cancer of the stomach is too high, particularly in relationship to cancer elsewhere in the body. Over approximately the same period which this survey covers there were 6,245 patients with cancer elsewhere in the body receiving radiation

treatment. These were grouped as follows:

Female genitalia	2,515
Breast	1,014
Skin	486
Male genitalia	477
Mouth	425
Upper respiratory tract	313
Genitourinary (both sexes)	291
Lungs	246
Skeleton	154
Lymph nodes	94
Miscellaneous	230

The roentgen-ray opinion of malignant tumor has been advanced in 2,625 diagnostic cases, exclusive of the gastrointestinal tract. In the diagnostic figures, there was present on roentgen examination of the lung 559 carcinomas of that organ. This does not include the metastatic tumors.

An astonishing fact is that in the thirty-one years covered by this study there have been but two correct roentgen diagnoses of carcinoma of the small intestine. In this same period in a total of 192,536 hospital admissions[4] there were only 7 additional small intestinal cancers. Only 2 had a correct preoperative roentgen diagnosis in this series, and 1 had the examination made elsewhere. There was 1 incorrect diagnosis —perforation of the duodenum, which was caused by a carcinoma. The remainder were found at autopsy or at surgical operation for obstruction or perforation. The incidence of the different portions of the small intestine was: 2 of the ileum, 3 of the jejunum, and 3 of the duodenum.

It seems safe to conclude that with the present state of the art of gastrointestinal examination it must still remain an art and is therefore not suitable for mechanization such as would be the case with mass survey film techniques. Although there might be some possibility of detecting cancer of the stomach with this method, it probably would detect only the late cases. The accepted method of examination by the radiologists of this country is highly efficient, and gastric cancer of the one type which seems to be suitable for detection by mass survey methods comprises but a small part of the malignancy problem and even a relatively small part of the incidence of gastrointestinal cancer.

From the data which have been accumulated, it is obvious that overemphasis has been placed on the incidence of cancer of the stomach. It is, of course, true that different data will be found in different clinics, but on the whole, sight must not be lost of the fact of the terrifically high rate of cancer of the female breast, the uterus, and the lungs.

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PARAPLEGIC NEUROARTHROPATHY*†

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THE purpose of this communication is to call attention to certain neuropathic articular and periarticular changes occurring in the lower extremities of paraplegics. Their condition, as is well known, is a paralysis of the lower half of the body due to disease or injury of the spinal cord. This discussion concerns itself primarily with cases of transection of the cord due to gunshot wound or fracture of the spinal column since the patients observed were nearly all veterans of World War II. The manifestations of paraplegia, i.e., spastic or flaccid paralysis of the lower extremities, anesthesia generally waist high, paralysis of the bladder and rectum, and intractable bed sores, are so devastating that changes in and about the joints of the lower extremities are usually overlooked or ignored.

Historically, joint changes due to spinal cord injury were mentioned by Charcot in 1868 as a part of his original description of the neuropathic joint which bears his name. The neuroarthropathy of Charcot is also etiologically related to a variety of other neurological diseases, such as tabes, syringomyelia, diseases of the spinal column and cord, trauma to the posterior roots, spina bifida, peripheral nerve injuries, and hemiplegic states. The term "Charcot's joint" includes a variety of joint manifestations, some of which are as dissimilar grossly as their variable etiology. In a general way, this arthropathy is divided into two major groups, the hypertrophic and the atrophic forms. The former is characterized by erosion and fragmentation of the articular extremities and intraarticular and periarticular ossification. In some cases the intraarticular changes predominate, and in others the periarticular changes do. The latter are believed to result from the abnormal stresses and strains placed on the periarticular muscular and connective tissue structures by the unstable fragmented joint.[11] The atrophic Charcot joint differs vastly in appearance from the hypertrophic form. Instead of massive enlargement and fragmentation of the articular extremities and periarticular ossification, one finds in this arthropathy, which is seen especially in the shoulder and hip, erosive enlargement of the socket part of the joint, erosive absorption of the articular extremity of the humerus or femur, as the case may be, and relaxation of the capsule and ligaments, producing the typical "drumstick" appearance. Periarticular ossification is also minimal in this form of arthropathy.

The most common causes of Charcot's joint are tabes dorsalis, in which joint changes occur in from 4 to 10 per cent of cases, and syringomyelia, in which joint changes usually occur in about 25 per cent of cases.[11] In tabes both the atrophic and hypertrophic forms occur, whereas in syringomyelia the atrophic form is most common.

The variable joint changes which are grouped under the term "Charcot's joint" are considered to have the one common feature of occurring in patients with neurological disease. There has, however, been considerable dispute as to the underlying

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† The recent article by Heilbrun and Kuhn: Erosive bone lesions and soft tissue ossifications associated with spinal cord injuries (paraplegia), *Radiology*, 1947, *48*, 579, was published after our paper was completed. These authors stress erosive bone changes in the greater trochanters. This was seen in one of our cases, but was considered to be a part of the erosive process associated with the development of an atrophic Charcot joint. These erosions of the greater trochanters undoubtedly occur more frequently than our small series would indicate, but this does not alter our conclusions as to the nature of paraplegic articular and periarticular changes.

Fig. 1. Case 1. C.E.C., aged twenty-four, gunshot wound of tenth and eleventh dorsal vertebrae on March 23, 1944, with subsequent spastic paraplegia, sensory loss, neurogenic bladder and decubitus ulcers. Roentgenogram taken on June 17, 1946, shows small bony plaque on the outer aspect of the left greater trochanter. Right hip was negative.

mechanism of these joint changes. The mechanical theory advanced by Volkmann attributes the joint destruction to the trauma associated with the continued use of an ataxic joint which lacks certain forms of sensation, or is completely anesthetic. Opposed to this theory is Charcot's original idea that the joint conditions are due to disorder of the normal neurotrophic impulses originating from the central nervous system in these neurological diseases, which impulses are necessary for the normal nutrition of the part. As evidence for the mechanical theory is the experimental work of Eloesser, who demonstrated that trauma in the limb of a cat rendered anesthetic and analgesic experimentally leads to grotesque lesions of the bones and joints which are in every way counterparts of tabetic fractures and arthropathies.[5] It is not proposed to enter into a detailed discussion of the pros and cons of the two theories, but it is sufficient to say that the burden of evidence appears to be in favor of the mechanical theory.

Paraplegia due to disease or injury of the spinal cord has received little notoriety as a cause of neuropathic articular and periarticular changes. Considerable emphasis has been placed in the French and German literature since the first World War on a condition described by the French as a paraosteoarthropathy[1] and by the Germans as a neurogenic myositis ossificans,[6,7] occur-

Fig. 2. Case 11. M. W., aged twenty-eight, fracture of the fifth cervical vertebra in August, 1943, with development of partial paralysis of arms, spastic paralysis of legs, neurogenic bladder, and decubitus ulcers. Roentgenogram taken on June 24, 1946, shows beginning ossification adjacent to the outer aspect of right greater trochanter. Left hip was negative.

ring about the hips and knees of paraplegics. These periarticular ossifications were classified with myositis ossificans rather than with the Charcot arthropathy, although it was recognized that the typical Charcot joint with both intra- and periarticular changes occasionally was seen in the paraplegic and that gradations between the two conditions occurred.

Many theories as to the etiology of this periarticular ossification were offered. It was recognized that fundamentally the condition was related in some way to the lesion in the spinal cord. Some believed that irritative neural impulses set up by the spinal cord were responsible for the soft tissue ossification.[6] Others believed that physical and chemical changes occurred in the paralyzed muscles as a result of edema of the lower extremities,[8] atrophy and degeneration of the muscle fibers,[3] microscopic hemorrhages into the paralyzed muscles, etc.,[3] which resulted in muscle ossification. Inflammatory changes in the muscles[8] possibly related to the deep bed sores were considered, but it has been shown that the ossifications have no anatomical relationship to the decubitus ulcers.[1] The likelihood of an individual diathesis to soft tissue ossification as originally advanced by Virchow to explain myositis ossificans was also brought up, and there is no doubt that some such concept in our present state of ignorance must be used to explain why only about 50 per cent of the cases show these changes. Metastatic calcification secondary to the osteoporosis of recumbency[6] has also been mentioned. However, many of these cases are not recumbent for more than several months, and the condition is actual ossification rather than calcification.

In addition to periarticular ossification in the soft tissues, occasional instances of variable destructive changes in the joints generally associated with the above have also been reported. These have been considered to be typical Charcot's joints,[1,2,7,12] some with hypertrophic manifestations predominant and others with atrophic changes.

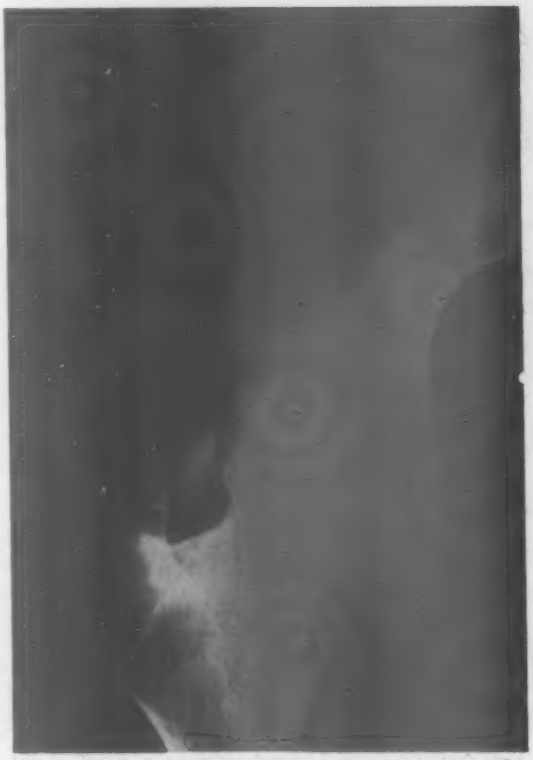

Fig. 3. Case III. C. E. B., aged twenty-four, gunshot wound, fourth dorsal vertebra, on January 10, 1944, and immediate spastic paraplegia. Had bed sores over sacrum, greater trochanters, anterior and inner aspects of knees and legs and over both heels. Only in recent months has he developed very slight swelling of the left thigh. Roentgenogram taken on August 13, 1946, shows slight new bone formation above the right greater trochanter. Left hip was negative.

One of our own cases showed periarticular new bone formation about a hip joint initially; but after a number of months, absorption of the head of the femur occurred and also enlargement of the acetabulum producing a classical atrophic Charcot's joint.

Not only may there be a more or less gradual transition between the neuropathic periarthropathy and the arthropathy of the paraplegic, but also between the hypertrophic and atrophic arthropathy of the tabetic. In the latter disease, a joint may initially assume the characteristics of a hypertrophic neuroarthropathy and later those of an atrophic joint.[11]

Fig. 4. Case iv. *A*, right hip; *B*, left hip. J. J. P., aged twenty-five, sustained a fracture of the lower cervical region on May 30, 1940, with immediate paralysis of both lower extremities and arms and loss of function of bowels and bladder. He had swelling of both entire lower extremities, much more marked below the knees, which began about three months after the injury and lasted one month. He had bed sores over the sacrum, left hip, on each heel, and over the left anterior superior iliac spine. Roentgenograms of both hips on June 19, 1946, were negative, but on May 16, 1947, they showed new bone on the outer aspect of both greater trochanters, more marked on the right side and at the attachments to the right lesser and greater trochanters.

Even though these various types of neuroarthropathy may appear to merge with each other and to have certain characteristics in common, the cause of the multiplicity of forms even when produced by a single neurological disease such as tabes has never been adequately clarified. Nor is it entirely clear why the changes in paraplegia are generally confined to periarticular soft tissue ossification, mostly about the hips. However, in the early stages of many of these paraplegic joints, ossification may be seen to begin on the lateral aspect of the greater trochanters, and this suggests that long-continued pressure over anesthetic bony prominences and lack of warning sensation are equivalent to trauma and initiate ossification in the periarticular tissues. The scarcity of intraarticular changes in the paraplegic may be attributed to lack of much use of the insensitive joint due to the additional factor of muscular paralysis,

FIG. 5. Case v. *A*, right hip; *B*, left hip. R. I. J., aged thirty-two, gunshot wound of the third dorsal vertebra in March, 1944. He had a spastic paraplegia and multiple bed sores. Roentgenograms taken on June 19, 1946, showed ossification in the soft tissues about both hips.

so that trauma to the intraarticular structures due to unphysiologic movement does not frequently occur.

In the literature, the soft tissue ossification in paraplegics, other neuroarthropathies, and traumatic myositis ossificans is considered to arise by metaplasia of existing muscular and connective tissue structures, and also by means of traumatic avulsion of shreds of periosteum.[1,6,9] The ossifications in paraplegia are located about the hip joints, attaching to the pelvis and trochanters of the femurs, and also in the muscles on the inner aspects of the thighs extending upwards from the medial femoral condyles. In some cases ossifications about the ankle joints also occur.

In our small series, consisting of 9 cases

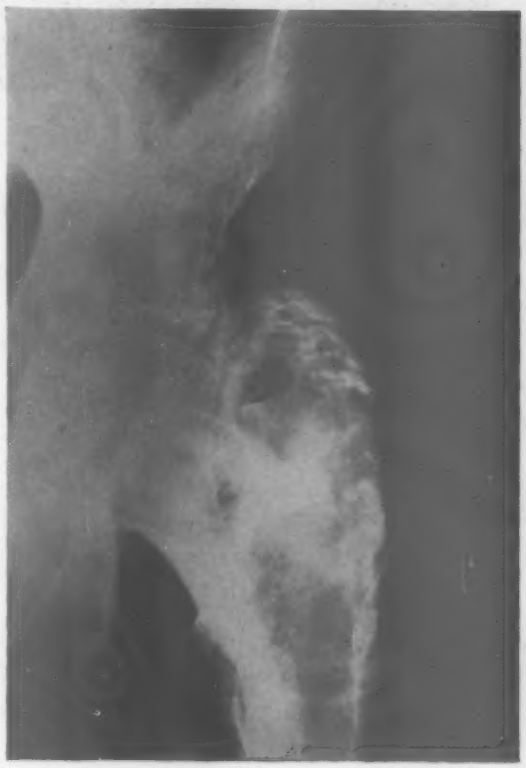

FIG. 6. Case vi. D. T. T., aged twenty-six, sustained a gunshot wound of the lower dorsal region in 1944. He had a flaccid paralysis, anesthesia, and multiple deep infected bed sores. Roentgenograms on November 21, 1945, showed lace-like ossifications attaching to both greater trochanters extending toward the pelvis.

with complete paralysis and anesthesia of both lower extremities, the hip joint regions only were affected. The changes consisted of small bony plaques adjacent to or contiguous with the greater trochanters, often bilateral and symmetrical. In several cases the bony outgrowths extended up toward the pelvis or into the muscles of the thighs. Only one case showed erosion of the articular surfaces characteristic of an atrophic Charcot's joint. All the patients showed slight osteoporosis, but only 2 showed severe osteoporosis of the pelvis and hips, one with periarticular ossification, and the other without it, but manifesting bladder calculi. Of the 9 cases, 7 showed some degree of periarticular ossification. It is felt that this percentage is unusually high and entirely fortuitous in that the figure of slightly less than 50 per cent given in the literature[1,3] probably more closely approximates the true state of facts. Of the 9 cases, 7 had a spastic paralysis and 2 a flaccid paralysis. Five cases were due to gunshot wound of the dorsal spine, 3 to fracture of the spinal column, and one to a meningioma in the dorsal region. Almost all the cases had bed sores of greater or lesser severity, but edema of the lower extremities was not a conspicuous feature of any of the cases at any time.

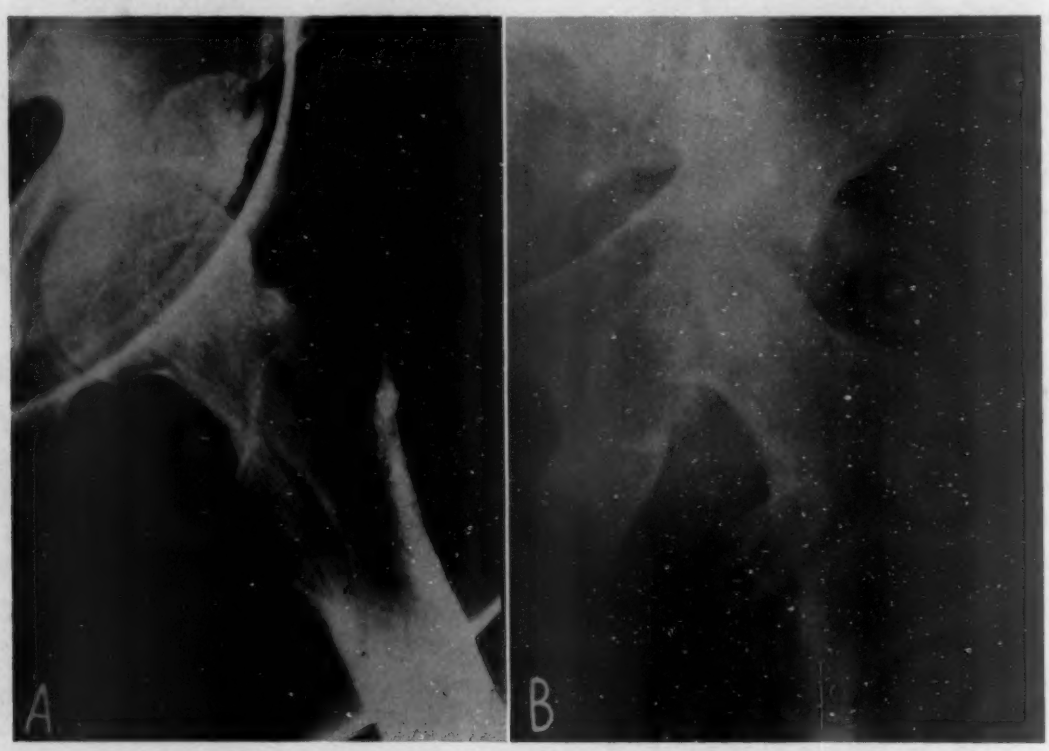

Fig. 7. Case vii. D. D., aged twenty-six; fracture dislocation of the twelfth dorsal vertebra on November 19, 1945, with flaccid paralysis and anesthesia. Left leg had to be amputated at mid-thigh level. His right foot swelled slightly for about a month after the injury but not since then. He had bed sores over the sacrum, greater trochanters, iliac crests, head of right fibula, right heel and outer aspect of right foot and lower leg. Roentgenograms taken on June 24, 1946 (*A*, right hip), showed ossification in the soft tissues about both hips. On April 10, 1947, the left hip was unchanged, but the right hip (*B*) had developed into a typical atrophic Charcot's joint with erosion of the head of the femur, acetabulum and trochanters. There was considerable osteoporosis.

Teleologically speaking, the periarticular ossification might be considered to serve as an internal splint for the paralyzed joints

in the same way that Steindler has postulated that the ossification about an unstable tabetic joint may act as a splint.[11] Unfortunately, the ossification is rarely complete enough in the paraplegic to serve as such, although circumferential ankylosis of a hip joint has been described.[1] In addition, the joint may be fixed in an unfavorable position. It is therefore concluded that in the paraplegic, the ossifications and joint changes, when they occur, are not in in any sense purposive or desirable but merely neuropathic changes in an anesthetic paralyzed member, related to the neuroarthropathies of other neurological diseases.

SUMMARY

Neuropathic articular and periarticular changes occur in the lower extremities of paraplegics, constituting another example of the Charcot neuroarthropathy. In Charcot's joint, there may be intraarticular destructive and productive changes and also extraarticular soft tissue ossification—the hypertrophic variety; or there may be erosion and absorption of the articular extremities with relaxation of the capsule and ligaments—the atrophic variety. Periarticular ossification may be massive or minimal in either type. In the parapelgic, periarticular ossification is the outstanding feature, and intraarticular destructive changes are minimal or absent, though occasionally striking. Transitions between the various forms of neuroarthropathy may occasionally be seen.

The mechanism of the paraplegic neuroarthropathy is believed to be long-continued pressure over anesthetic bony prominences and lack of warning sensation, which are equivalent to trauma in initiating ossification in the periarticular tissues. The scarcity of intraarticular changes is attributed to lack of use of the paralyzed joints.

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DOUBLE CONTOUR, CUPPING AND SPURRING IN ROENTGENOGRAMS OF LONG BONES IN INFANTS*

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VERY little has been written on roentgen diagnosis in children in this country, and Caffey mentions in his book, "Pediatric X-Ray Diagnosis"[1a]: " . . . As far as I have been able to determine no book on pediatric roentgen diagnosis has been published in English during the 35 years which have passed since Rotch's unique publication in 1910."[2] Indeed a search through the literature in this country and abroad produced very few publications referring to normal roentgenograms in children, especially of the bones.

The purpose of this paper is to describe findings consisting of a "double contour," "cupping" and "spurring" seen on routine roentgenograms of the long bones, findings which have certainly been observed by roentgenologists and pediatricians who have the opportunity of seeing large numbers of roentgenograms of normal babies. These findings, to my knowledge, have not been discussed thoroughly in the literature and frequently lead to misinterpretation.

The only reference to these roentgen findings in the medical literature was found in Caffey's book: " . . . the ulna and occasionally the radius may form a curved (cupped) transverse surface instead of the usual straight plane at right angles to the long axis of the shaft. This physiologic cupping has been described in many nonrachitic infants. . . . "[1b] " . . . The interosseous ridge on the medial side of the shaft may cause an extra shadow which simulates asymmetrical subperiosteal cortical thickening . . . "[1c] " . . . On the superior aspect of the lateral margin of the tibial shaft, the ridge for the insertion of the tibialis anticus muscle should not be misconstructed as a regional thickening of the cortex."[1d]

Unfortunately, however, the book fails to show illustrations of these findings, nor does it give a numerical interpretation of the frequency and time of occurrence or a pathologic investigation as to the reason for the appearance of these pseudo-pathologic findings.

McLean and McIntosh[3] in 1928 made the following statement: " . . . Another source of difficulty in the interpretation of spurs arises from the fact that the zone of preparatory calcification actually presents in the x-ray the projected shadow of a disk. . . . "

These were the only references which could be found, and even complete works such as Wimberger's[4] clinical-roentgenological diagnosis of rickets, scurvy and syphilis, Rotch's[2] book or Köhler's Röntgenology[5] do not mention these observations.

The tables of our study bring a report of 100 consecutive prematurely born babies observed at a Premature Follow-up Clinic at Cook County Children's Hospital during the years 1945–1947. Roentgenograms of the long bones, wrists and ankles were taken routinely at monthly intervals up to their eighth month of life. Thus the total number of roentgenograms viewed is approximately 800. The growth and development of these babies were apparently normal.

In viewing these roentgenograms we have noticed several findings on long bones of these infants which were in the beginning frequently interpreted by us and by others as signs of rickets, scurvy or congenital

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syphilis. The large number of roentgenograms taken, however, and the close supervision and study of these babies led us to the conclusion that these findings were physiologic and that their interpretation as signs of pathology was incorrect. This was later proved by the fact that the forearms of the child were placed flat on the film in pronation, thus getting a postero-anterior view of the forearms and hands, parallel position of the ulna and radius and good visualization of the distal epiphysis. The lower extremities were placed in a lateral position on the film in order to pro-

TABLE I

MONTH OF FIRST VISIBILITY OF "DOUBLE CONTOUR" (100 INFANTS)

Bone	1st	2nd	3rd	4th	5th	6th	7th	8th	Total
Ulna	*	*****	********	********	********	********	**	***	78
		****	*******	********	***	********			
				***		**			
	1	9	15	19	11	18	2	3	
Radius	*	***	********	********	********	********	*****	****	76
			*******	********	**	*******			
				*******					
	1	3	15	23	10	15	5	4	
Tibia	*	****	********	********	******	******	*		49
			********	****					
			***						
	1	4	19	12	6	6	1		
Fibula			*****	********	****	*****	*****	*	28
			5	8	4	5	5	1	

MONTH OF FIRST VISIBILITY OF "CUPPING" AND/OR "SPURRING" (100 INFANTS)

Ulna		***	********	********	********	********	*	***	73
			********	********	*****				
			********	****					
		3	* 25	20	13	8	1	3	
Radius			********	********	********	****	*	***	46
				********	****				
			8	** 18	12	4	1	3	
Tibia			** 2	*** 3	* 1	*** 3			9
Fibula			* 1	*** 3		** 2			6

Note: Each asterisk indicates a case which showed the "double contour," "cupping," or "spurring" for the first time during the respective month.

"double contour" as well as the "cupping" and "spurring" disappeared spontaneously without any change in management.

The technique of taking the roentgenograms was the routine method of "long bones, wrists and ankles" films. Hands and duce a view of the distal epiphysis of tibia and fibula. A true anteroposterior view would distort the picture of the epiphyseal line because of the distance produced by the protruding heel. The lateral view, unfortunately, does not permit a complete

Fig. 1. "Double contour" on ulna and radius in a five month old healthy prematurely born infant.

visualization of the fibula and tibia, as some parts of these bones are always overshadowing each other in this position.

The observations can be described in short as follows: The surfaces of the long bones of the forearm and shank were frequently outlined by a double contour which gave the impression of periosteal thickening or elevation and/or cortical hypertrophy. These lines may be present on all four bones of the distal parts of the extremities or on only one or more; they were seen most frequently on the ulna, and with decreasing frequency on radius, tibia and fibula (see Table 1). Frequently they appeared on one bone first and became visible on some of the other bones as well on roentgenograms taken one or more months thereafter. These lines may cover the entire length of the bone, from metaphysis to metaphysis, or may be very short, beginning at one end of the bone, emerging from the periosteum, paralleling it in about 0.5 to 1.0 millimeter distance and fading into the subcortical structures. The line itself is usually smooth, but occasionally shows thickening or thinning of its shadow (Fig. 1 and 2). In the largest number of cases this double contour was observed for the first time during the third or fourth month of life. In following up these findings we noted that the lines began to be less frequently visible around the seventh and especially the eighth month of life (Table 11).

A second observation was the peculiar appearance of the epiphyseal line, showing some characteristics which at times may be interpreted as signs of disease. The orthodox picture of the epiphyseal plate is a straight line. However, if the roentgen rays traverse the epiphyseal plate at an angle other than a right one, it may appear concave or convex and the edges will then

Fig. 2. "Double contour" on tibia and fibula in a seven month old healthy prematurely born infant.

seem elongated, which resembles the "spurring," "lipping," or "cupping" as seen in scurvy and rickets. At times bizarre pictures of waves or ellipses may be seen (Fig. 3 and 4). This "cupping" and "spurring" became first visible in most cases around the third and fourth month of life and began to disappear in many cases around the seventh and eighth month (Tables I and II). The reason for this disappearance in later life is probably the fact that the more intense calcification of the bone does not permit penetration of the rays in these older babies and thus prevents the visualization of a second shadow. This will be further elaborated later.

It should be noted that these above mentioned figures (Tables I and II), although probably true enough to give a good account of the frequency at which these phenomena can be observed and therefore of the chances for misinterpretation, may not be accurate if taken from a purely statistical point of view. To explain this fact, some of the shortcomings in the technique may be mentioned here. If the lower

TABLE II

MONTH OF DISAPPEARANCE OF "DOUBLE CONTOUR" (100 INFANTS)

Bone:	1st	2nd	3rd	4th	5th	6th	7th	8th	Total
Ulna			*		**	***	******	******** ******** ****	32
			1		2	3	6	20	
Radius			*			******	****	******** ********	27
			1			6	4	16	
Tibia				*		******	****	******** *****	24
				1		6	4	13	
Fibula						**	*	*****	8
						2	1	5	

MONTH OF DISAPPEARANCE OF "CUPPING" AND/OR "SPURRING" (100 INFANTS)

Ulna					*	****	******** ********	******** ******** ******** ******	51
					1	4	16	30	
Radius				*	*	****	*******	******** ******** ***	32
				1	1	4	7	19	
Tibia						**	*	******	9
						2	1	6	
Fibula								*****	5
								5	

Note: Each asterisk indicates a case which for the first time during the respective month *failed to show* the previously visible "double contour," "cupping" or "spurring."

Fig. 3. "Wavy" epiphyseal line of tibia and fibula in a five month old healthy prematurely born baby.

legs are viewed in a true anteroposterior position, the heel of the foot, especially in Negro children, will prevent the parallel apposition of the fibula and tibia to the film. The result is a distorted, not sharply outlined view of the distal epiphysis, which does not permit the interpretation of the epiphyseal line. On the other hand, if we take a lateral view of the lower leg, which in general was done, the epiphyseal lines were well outlined and visible, but the shadow of the tibia and fibula were partially or totally overlying, thus prohibiting a true interpretation of the periosteum and the "double contour." We were unable to fully overcome this difficulty, but did not find any special need for doing so. In the individual case two roentgenograms, one in true anteroposterior and one lateral, or one well placed oblique view, would answer the problem. We may also add at this point that due to technical difficulties, such as

Fig. 4. "Cupping" and "spurring" seen in the roentgenogram of right ulna but almost unnoticeable on the roentgenogram of the left ulna of a three month old baby, taken at the same time but with slightly different angle.

movement of the patient during exposure, and so forth, certain views were missing, which may further alter the exact numerical relationship of appearance, disappearance and incidence. We do not believe, however, that any of the above-mentioned shortcomings would alter the sense or interpretation of this paper materially.

In order to compare the findings on our premature infants with findings on full term babies, an unselected group of 100 patients, admitted to the Hospital for various reasons obviously unrelated to the growth or development of the bones, was chosen and the same type of roentgenograms as of the premature group were taken. The infants' ages ranged from one to eight months. One roentgenogram was taken of each infant. Of 67 babies who fell into the age group from two to six months, double contour was seen on the ulna in 46, on the radius in 37, on the tibia in 24 and on the fibula in 14 roentgenograms. The incidence of the visibility of these lines during the first, seventh and eighth months was considerably lower. Spurring and cupping was found most frequently between the third and fifth months. The total incidence of spurring and cupping was lower in this group than in the premature babies. This sample group of average newborn to eight month old infants demonstrates that the "double contour," "cupping" and "spurring" are not a characteristic of the premature baby, but occur in the full term child as well.

Although statistically the group of full term infants is not comparable with the group of premature babies, because only one roentgenogram was taken of each of the full term babies and thus the "first appearance" was not determined but only the general incidence, the figures show that the "double contour" tends to occur earlier (second month) and to disappear earlier (fifth month) in the full term babies, as would be expected because of their higher degree of maturity and greater density of calcification of their bones.

The occurrence of a "double contour," "cupping" and "spurring" was also studied on a smaller number of roentgenograms of femur (56) and humerus (42) of the same groups of premature children. The double contour was found to be less frequent in this group (femur 17, humerus 15). This lower incidence corresponds to the rounder form of the transverse section of these bones which will not so readily permit the appearance of a double shadow. The cases in which double lines were seen were due either to the increased prominence of the posterior crests, to clearer separation of cortex from marrow, or to a clearly visible canal of the nutrient artery. The absence of "cupping" of the distal epiphysis of the humerus and femur is easily explained by the convexly curved character of the epiphyseal plate.

The small number of roentgenograms of full term babies prohibits numerical evaluation of the incidence of these phenomena in this group, but suffices to prove their existence.

Extensive examinations of the blood, chemically, for calcium, phosphorus, phosphatase, and serologically, of the babies used for this study, did not reveal any signs of pathology. The graphic and statistical evaluation of the growth and development of these babies proved their normal progress as compared with standard figures. A histopathological examination of the cross-sections of all four bones (radius, ulna, tibia, fibula) of one of the babies who showed the above described double lines and died of interstitial pneumonitis also revealed normal structure as shown by the pathologist's report: "The microscopical examination of the sections taken from the tibia, fibula, radius and ulna showed normal spongiosa and compacta. The periosteum was of appropriate thickness and structure, no inflammatory reaction (exudation, congestion of vessels, proliferation of connective tissue) was observed. The architecture of the bony structures was normal, the bone marrow showed myelo-erythropoietic activities."

The explanation of these double lines

can be made by a careful observation of the anatomical structure of the bones, especially their crests and the direction of the roentgen rays in relationship to the bone and the film (Fig. 5).

The more intense shadow of the cortex of the shaft will produce occasionally a line parallel to the outer contour of the bone and visible mainly in the middle third of the shaft. On certain films the canal of the nutrient artery of the bone can also produce a similar effect. This last phenomenon, however, does not give rise to misinterpretation by the experienced. The much less frequent visualization of the double line in the tibia (49 per cent) and the fibula (28 per cent) as stated in our table, may not only be attributed to the different shape of the cross-sections of these bones but also to the technical difficulty of good visualization of the entire outline of both bones as described above.

The explanation of "cupping" and "spur-

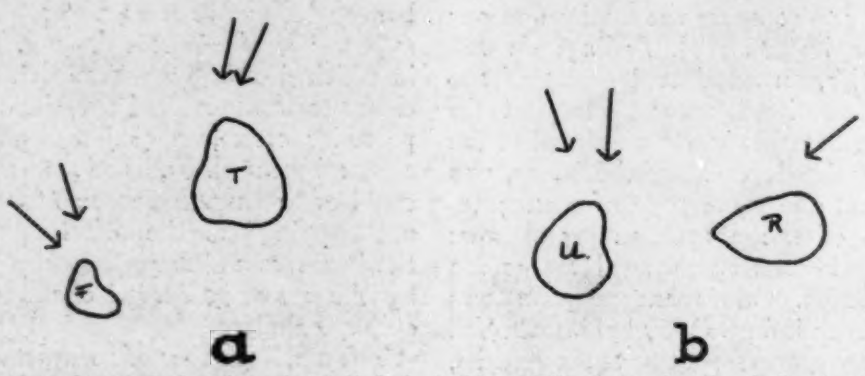

Fig. 5. Drawing of cross-section through (*a*) fibula and tibia and (*b*) ulna and radius, indicating the arrangements of crests running along the anterior, lateral and medial aspects of the bone which may, under a certain relationship of the position of tube, bone and film, as indicated by the arrows, produce a double line.

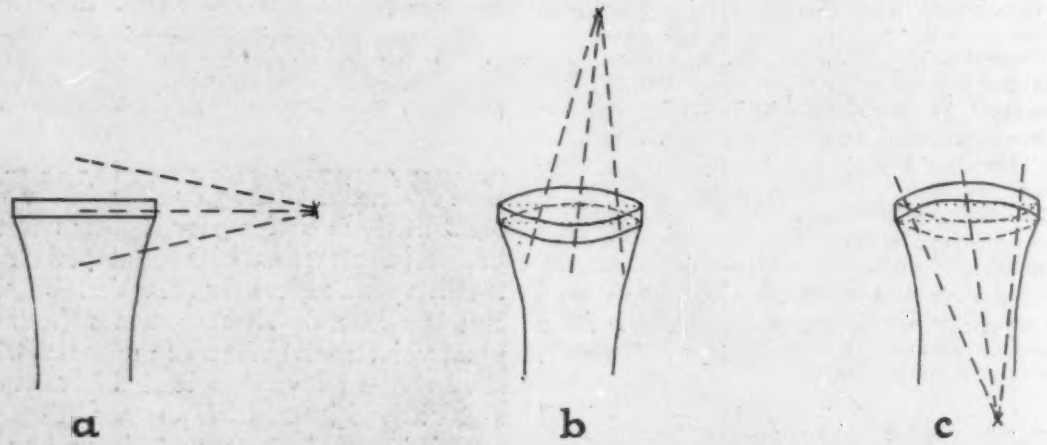

Fig. 6. (*a*) Rays hitting parallel to the epiphyseal plate produce a straight line; (*b*) and (*c*) Rays hitting at acute angle will produce an appearance of cupping or bulging depending upon degree and direction of opening of angle.

ring" may also be found in the projection of the anatomical form of the epiphyseal plate (Fig. 6).

For further study and better demonstration the radius, ulna, tibia and fibula of a four and a half month old, prematurely born infant who died of a condition unrelated to bone growth, were removed at necropsy, freed of most adherent soft tis-

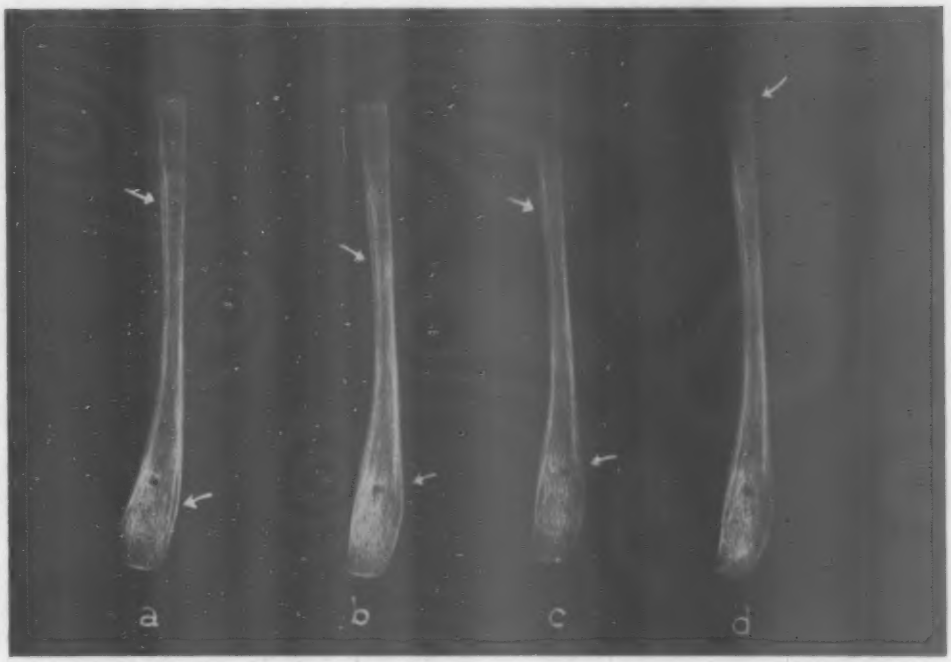

Fig. 7. *Right ulna* (*a*) turned 15 degrees to the left of the true anteroposterior position: double line visible on lateral aspect of proximal third and medial aspect of middle third of bone; (*b*) true anteroposterior position: same double lines visible but less pronounced; (*c*) inclined 15 degrees to the right: double line on proximal third has practically disappeared; line in the middle third is better visible than in (*a*) and (*b*); (*d*) anteroposterior position with the roentgen tube placed distal to the bone and focused on the bone at an angle of 20 degrees: epiphyseal plate projects in form of a curved line (cupping) whereas (*a*), (*b*) and (*c*) show it projected essentially as straight line.

(The dark spot in center of proximal third of bone is an artefact and was produced by a drill perforation in an attempt to find a method for stabilization of the bone and exact measurement of the angle. The final technique used was the fixation of a wooden stick to the bone and a vertical wire attached to the stick as pointer. This permitted accurate measuring of wire's and thus bone's angle in relation to the tube.)

sues, and studied roentgenographically and histologically.

The following roentgenograms (Fig. 7, 8, 9 and 10) demonstrate the visible "double line" and also the "cupping" and "spur-

Fig. 8. *Right radius:* (*a*) in anteroposterior position with tube directly above bone: epiphyseal plate projects at straight line; (*b*) in anteroposterior position, with roentgen tube placed distal to the bone and focused on the bone at an angle of 20 degrees: epiphyseal plate now projects as curved line.

(The soft tissue shadow distal to the radial epiphysis was produced by the incompletely removed joint capsule.)

ring" as indicated by arrows. These findings are better visible on roentgenograms taken of the bone removed from the body and cleared of its soft parts than on the roentgenograms of the extremity in vivo. This experience will enable the reader to acquaint himself with the described lines and to recognize them more readily on the ordinary roentgenogram. To show that and how these lines vary if the angle between rays and bone is changed, a series of roentgenograms was taken at different positions. It is evident from these roentgenograms that the intensity, position or length of the double contour or the appearance of the projection of the epiphyseal plate varies with the position of the roentgen tube. This explains the fact that only a certain number of "routine roentgenograms" will actually show these phenomena and that changes in the position of patient and tube, which to a minor degree occur constantly on "routine roentgenograms," will be responsible for the more or less frequent appearance and the variation in different bones of children of the same age group.

Fig. 9. *Right tibia*: anteroposterior position with the tube (*a*) accurately above the bone (straight epiphyseal line projection); (*b*) distal to the bone, focused on the bone at an angle of 25 degrees (convex epiphyseal line projection); (*c*) proximal to the bone, focused on the bone at an angle of 25 degrees (concave epiphyseal line projection).

The data in Tables I and II were arrived at by the study of a large number of roentgenograms taken at various times by different technicians, and indicate only the incidence of the visibility of the above phenomena in the roentgenograms and not the absence or presence of an anatomical structure. The two tables demonstrate very well, however, the relative frequency of occurrence during certain months of the child's life. The explanation for this temporary visibility may well be the poor calcification of the entire bone which prohibits visualization of the crests during the first weeks of life; the increased formation and calcification of prominences during the following months and the still relatively roentgen transparent bone permit the visualization of the above described phenomena at this time. Progressive calcification of the entire bone in the subsequent period decreases the visibility of finer details and thus causes the disappearance of the findings. The period from three to six months of life in our premature infants and roughly from two to five months in full term babies corresponds to this interim period during which "double contours," "cupping" and "spurring" can be seen with greatest frequency, and it is also this age period during which the differential diagnosis of congenital syphilis, scurvy and rickets has to be taken into special consideration.

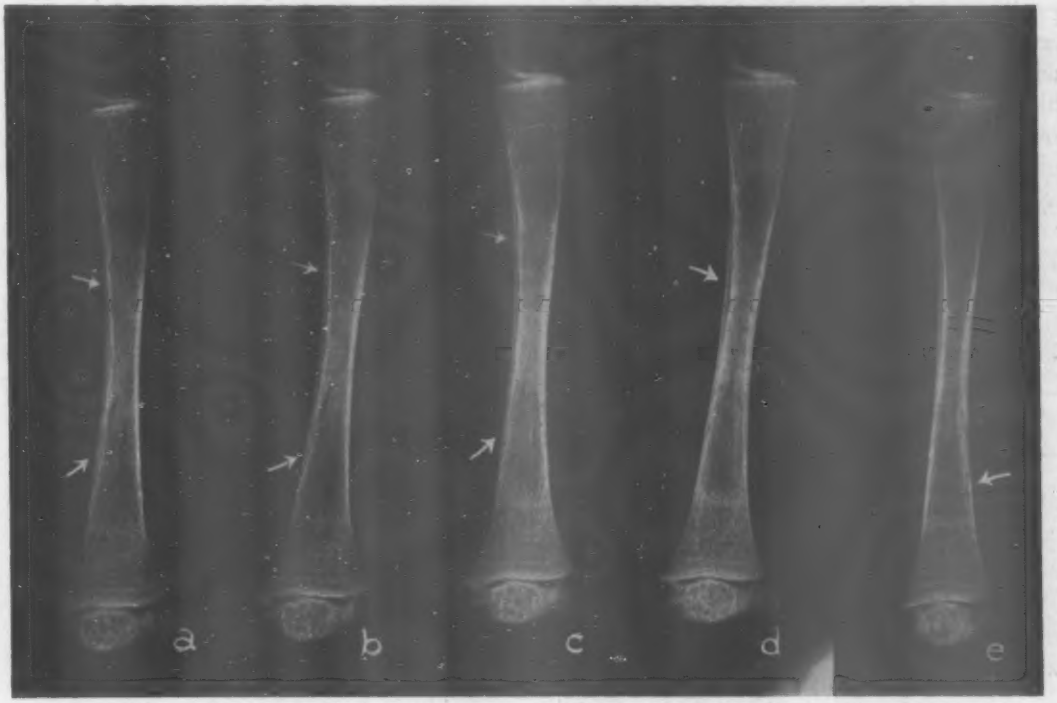

FIG. 10. *Right tibia* (*a*) turned 25 degrees to the right of the true anteroposterior position, showing double line on medial aspect of middle third and on proximal third; (*b*) turned only 15 degrees in the same direction makes line in middle third better visible but reduces visibility of line in proximal third; (*c*) true anteroposterior position: line in middle third well visible, in proximal third line has almost disappeared; (*d*) turned 15 degrees to the left: line on middle third well visible but progressively shorter; proximal line no longer visible; (*e*) turned 25 degrees to the left: a new "double line" appears on lateral aspect of proximal end.

Microsections, prepared from the same bones after the above roentgenograms were

taken, demonstrate the normal structure of the bone as seen from the report of the pathologist: *Transverse section*—cortex and spongiosa show normal architecture. Periosteum is of normal thickness. *Diagonal section*—at the epiphyseal line the cartilage shows the typical arrangement into resting, proliferating and columnar zone of cartilage cells. The bone trabeculae are of normal width. The primary bone marrow cavity is filled with normal bone marrow. The *section* in the *frontal plane* shows the typical picture of endochondral ossification. In the hyaline cartilage the cartilage cells are arranged in columns in a typical fashion. The zone of proliferating cartilage cells is of normal width. Nearer the zone of ossification the flat cartilage cells are swollen. The metaphysis is composed of spongy bone substance consisting of trabeculae of normal width, arrangement, and mineral content. The bone corpuscles show the orderly arrangement of bone corpuscles in normal ossified tissue. *Summary:* The sections taken in various directions reveal the regular sequence of events characterized by proliferation of cartilage cells and conversion of the osteoid tissue into regular bone.

SUMMARY

Monthly roentgenograms of 100 healthy, prematurely born infants from birth to eight months were viewed and studied. A double line in the contour of the long bones of the extremities and a cupped and spurred appearance of the epiphyseal line of the same bones were observed frequently. These phenomena may be misinterpreted as signs of a pathological process. However, we have tried to demonstrate that these findings do occur in healthy premature and full term infants, that histopathologic examination of sections through the bones of infants who showed these lines in vivo and died of unrelated conditions are also normal, that they are most frequently seen in the age group from two to six months and that their later disappearance occurs without any treatment or change in management, and that the findings can therefore be considered as a normal roentgen appearance of the long bones during the process of growth.

I wish to express my appreciation to Dr. John Caffey, Babies Hospital, New York, for his valuable suggestions which helped materially in the completion of this paper, and to Dr. P. R. Szanto, Department of Pathology, Cook County Hospital, for procuring and interpreting the pathologic specimens.

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Vol. 61, No. 4

SESAMOID BONES OF THE HANDS AND FEET

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IN 1940 Francis[9] presented Brush Foundation data for the appearance of ossification centers from 6 to 15 years. In the course of that study he observed the sesamoid bones to be more numerous in the females of the fifteen year age group. At Dr. Francis' suggestion this author began an investigation of the sesamoids of the hands and feet to see whether or not a definite sex-limited factor existed. The scope was then broadened to include a general review of the sesamoids of the hands and feet.

From the files of the Brush Foundation, Western Reserve School of Medicine, roentgenograms of 529 hands and 510 feet were reviewed. Young adults who had reached, or nearly reached, maturity, according to the Todd method of assessment of skeletal age were used. Cases were selected at random from the files according to age, excluding only those cases which showed definite endocrine disturbances. All roentgenograms examined were of the left extremity. Table 1 shows the sex distribution of the cases reviewed:

TABLE I

		Hands	Feet
18–30 years	White males	299	286
18–30 years	White females	230	224
TOTALS		529	510

HISTORICAL

The sesamoid bones, resembling grains of Indian wheat, are certain very round small Bones, somewhat flat and spongy within. They adhere at the Joynts to the tendons of the muscles that move the fingers and toes, and with them in the boyling of dead Carkasses, and the purgation and denudation of the bones are utterly lost unless great care be taken to preserve them.

It would be a difficult matter to find in any modern textbook of anatomy an account so full and good of these curious little bones as that given by Diemerbroeck (1609-1674), from whose work this quotation was made by Jones.[15]

The study of sesamoid structures, due to their size and frequent variations, has attracted of late but little attention. The medial sesamoid bone of the big toe has been identified by Garrison[10] as the bone "Luz," a mythical bone believed in medieval times to be the indestructible seed from which the body would be resurrected on the Day of Judgment.

The term "sesamoid" denotes the similarity between the size and shape of the bones, and that of the flat, oval seeds of the *Sesamum indicum*, an ancient East Indian plant used by the Greek physicians for purging. The name is said to have been applied by Galen.

Pfitzner,[22] in 1892, published his classical exhaustive monograph on the sesamoid bones and their variations, from dissection data of many cadavera, including 1,440 hands. The first correlation between the anatomical dissections and roentgenography of these bones was presented by Fawcett[7] in 1896. Of interest is his reaction to the clarity of early roentgenograms:

> Through the kindness of Mr. Chattock, Professor of Physics in University College, who has shown the greatest possible interest in the subject, I have been able to examine the hands of thirty-eight of my own students, and three of his by means of skiagraphy. The results exceeded in every way my fondest hopes. Not only were sesamoid bones clearly portrayed, but the cancellous tissue of the various bones was depicted in a delightfully clear manner.

ANATOMIC CONSIDERATIONS

Thilenius, cited by Lapidus,[19] proved conclusively the presence of cartilaginous anlagen for the two sesamoids beneath

each metacarpal head in a number of human embryos at about the third or fourth month. Inge and Ferguson[14] studied the development of sesamoids of the feet in the human fetus ranging in age from 8 weeks to 9 months. At the eighth week they found that both sesamoid bones are recognizable as islands of undifferentiated connective tissue in their normal location beneath the first metatarsal head. At the tenth week this connective tissue can be recognized as precartilaginous, and at the twelfth week there is a definite center of chondrification. These changes occur simultaneously in sesamoids, phalanges and metatarsals. The connective tissue in which the sesamoids develop is seen to be continuous with the periosteum of the metatarsal proximally, and with that of the phalanx distally; by the third month this can be identified as joint capsule, and the fibers of the tendon invest the lower portion of the bone between the third and fourth months. By the fifth month these bones have their normal adult shape, and the development from then on is in size. At no time did they find any evidence of formation from cartilaginous buds from the phalanx.

In the adult hand, as a rule, there are five sesamoids. Two of these lie at the metacarpophalangeal joint of the thumb in the tendinous insertion of the flexor pollicis brevis and the adductor pollicis. They are blended with the palmar ligament of the joint, and articulate with the palmar surface of the metacarpal bone. One sesamoid may be present at the interphalangeal joint of the thumb and two others at the metacarpophalangeal joints of the index and little fingers respectively. Sometimes not all five are present, and occasionally there are extra sesamoid bones in both the metacarpophalangeal and interphalangeal joints.

Lapidus[19] believes that, in the feet, sesamoids may occur in the lumbrical, and rarely in the interosseus tendons at the joint surfaces over which they act, an observation with which I concur, having noted several cases both in hands and feet which appeared to be in this anatomical location.

In the foot two sesamoid bones are almost constantly present at the metatarsophalangeal joint of the great toe. Each is enclosed by the corresponding tendon of the flexor hallucis brevis and the articular capsule, and articulates with and rests under the metatarsal head of the great toe, the cartilage of the latter being prolonged proximally for that purpose. The sesamoids are separated from each other by the tendon of the flexor hallucis longus. Between the sesamoids and the skin there is, normally, only the thick fibrous pad of the "ball" of the foot, through which the two small bones may occasionally be palpated. Not infrequently a bursa is interposed between the sesamoid and the skin. Other sesamoids occur at the other metatarsophalangeal joints, the interphalangeal joints and, occasionally, in the lumbricals and interossei. These will be discussed in greater detail in a later section.

The sesamoid and supernumerary bones of the carpus, tarsus and limbs are outside the scope of this presentation but Bizarro,[2] Dwight,[6] and Holland,[12] Burman and Lapidus,[5] and others, give excellent accounts of these interesting structures.

Lapidus[19] examined 320 extremities of various mammals in the New York Museum of Natural History; 56 fossils, 192 primates and 72 other mammals with special reference to the sesamoids. Two sesamoids were found beneath each metacarpal or metatarsal head in almost all adult specimens including the 56 extremities of the fossil animals.

It is difficult to give a conclusive reason for the existence of the sesamoid structures in the human body. Bizarro[2] in a remarkably complete study reviewed the comparative anatomophysiology and concluded that both phylogeny and function, combined, appear to be the two causes of sesamoid formation and development. The former originates and plants, as it were, the seeds for their formation, and the latter,

acting daily and with every movement, promotes the increase of size of these structures.

OSSIFICATION CENTERS

Ossification of the sesamoids has been studied extensively at this institution. The late T. Wingate Todd in his Atlas[27] described beginning ossification of the pollex sesamoids at about 12 years 9 months for males, and 11 years 9 months for females.

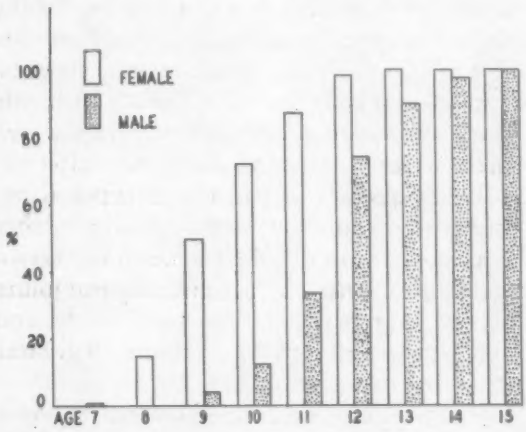

Fig. 1. Comparative time order appearance of ossification centers of the hallux sesamoids; showing percentage of ossification in males and females by years. (Courtesy of C. C. Francis.)

Todd[26] observed that there is a minor progressive acceleration of female skeletal maturation between 6 and 8 years. During the period 8 to 9 years the females slow up so that the male maturation reaches that of the female at about the latter date. At 10 years, the girls again advance ahead of the boys, and shortly after the thirteenth birthday are already at the stage reached in the boys about the fifteenth birthday. Thereafter, they slow down once more and at about 16.5 years the maturation of the male skeleton has finally caught up with the female.

Flory[8] found that 50 per cent of the girls in his series showed beginning ossification of the metacarpophalangeal sesamoid of the thumb at 11 years, and 50 per cent of the boys at 13 years. Francis[9] gives the comparative time order appearance of ossification centers of the pollex and hallux sesamoids as shown in Figures 1 and 2.

Ossification may occur from multiple centers which may, or may not, unite subsequently. Failure of union of these centers is believed to give rise to the partite appearance of these bones in the roentgenogram.

Baldwin[1] reported that sesamoids at the the thumb appear two years earlier in the

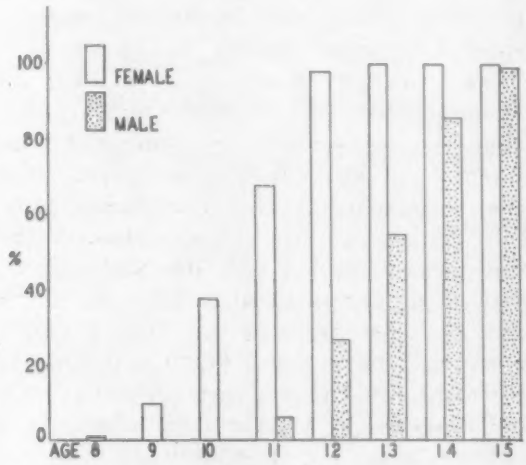

Fig. 2. Comparative time order appearance of ossification centers of the pollex sesamoids; showing percentage of ossification in males and females by years. (Courtesy of C. C. Francis.)

female than in male hands; from 10–14 years for girls and 12–16 years for boys. Flory[8] states that pubertal onset can be predicted fairly well by the appearance of the sesamoid bone at the distal end of the first metacarpal. This sesamoid appears in girls' hands about two years before the first menstruation. Buehl and Pyle[4] working in the Brush Foundation found that in 30 girls the average age of onset of ossification of the pollex sesamoids was 10.1 years; for 30 boys it was 12.6 years. They found that the mean menarche was 12.7 years for the 30 girls, these findings being in agreement with Flory. Rochlin, cited by Flory, concluded that sesamoids always appear before the sex glands begin their secretion in the endocrine system, before

Table II

PERCENTAGE DISTRIBUTION OF SESAMOID BONES IN THE HAND IN MALES AND FEMALES

	Thumb		Thumb	Index		Long		Ring		Little	
	R	U	IP	R	U	R	U	R	U	R	U
Males	100	100	60.5	39.8	0.3	0.0	0.0	0.0	0.3	1.7	77.6
Females	100	100	65.7	41.3	0.0	0.4	0.0	0.4	0.0	2.6	81.3
TOTALS	100	100	62.7	40.5	0.2	0.2	0.0	0.2	0.2	2.1	79.2

the final hairing, and before the appearance of menstruation.

SESAMOIDS OF THE HAND

It has previously been shown that the sesamoid anlagen are more numerous in the fetus than the definitive structures in later life. We assume that there is originally in the human hand a pair of sesamoids at each metacarpophalangeal joint, although not all have been observed in a single instance. In 299 male and 230 female hands the results in Table II were obtained, with each sesamoid anatomically designated radial or ulnar for convenience.

From the findings given in Table II, it is apparent that the sesamoids in the female hands are slightly more prevalent, but there is no significant difference. Kassatkin's[16] figures are in general agreement, with the incidence of the sesamoids of the females about 10 per cent higher in the index and little fingers.

(a) *Thumb.* In the reported series all radial and ulnar sesamoids or 100 per cent were found. Pfitzner[22] reported 99.9 per cent for the radial and 100 per cent for the ulnar. Bizarro[2] found that in 112 cases the metacarpophalangeal sesamoids of the thumb were missing in 2 instances, a percentage of 98.2. Kassatkin[16] in 1,096 hands studied, either by dissection or roentgenography, reported their presence as 100 per cent.

The sesamoids of the thumb may show bipartition. Pfitzner found this 3 times. Inge and Ferguson[14] studied 200 hands, and reported bipartition of the radial or ulnar sesamoid in 6 per cent of cases. They believe that, because these bones are not well seen in routine roentgenograms, the incidence is greater. In the 529 hands of this series, only 2 cases showed possible partition. Bizarro[2] was unable to find any evidence of bipartition of the pollex sesamoids.

In this series 62.7 per cent of cases had a sesamoid bone present at the interphalangeal joint of the thumb. This is in agreement with other authors. Pfitzner found that the interphalangeal sesamoid was rarely bipartite. Bizarro found a double interphalangeal sesamoid in one case, and I observed this in one case in the 529 hands reviewed.

In Table III the comparative findings of

Table III

PERCENTAGE DISTRIBUTION OF SESAMOID BONES IN THE HAND AS REPORTED BY THESE AUTHORS

	Thumb		Thumb	Index		Long		Ring		Little	
	R	U	IP	R	U	R	U	R	U	R	U
Pfitzner[22]	99.9	100	72.9	47.8	0.1	0.0	0.0	0.0	0.1	2.3	82.4
Fawcett[7]	100	100	68.5	55.2	0.0	0.0	0.0	0.0	0.0	0.0	71.0
Bizarro[2]	98.2	98.2	22.3	64.2	0.0	5.3	0.0	0.0	7.1	0.0	44.6
Kassatkin[16]	100	100	m-76.3 f-86.5	55.8	0.3	3.1	0.1	0.6	0.5	4.9	77.00

TABLE IV

PERCENTAGE ARRANGEMENTS OF SESAMOID COMBINATIONS OF THE HAND IN 529 CASES

	Thumb		Thumb	Index		Long		Ring		Little		Per Cent
	R	U	IP	R	U	R	U	R	U	R	U	
1	*	*	*	*							*	26.1
2	*	*	*								*	24.4
3	*	*									*	16.4
4	*	*	*								*	9.6
5	*	*										9.6
6	*	*	*									8.1
7	*	*	*	*						*	*	1.5
8	*	*	*	*								1.1
9	*	*		*								0.9
10	*	*	*					*			*	0.2
11	*	*	*	*		*					*	0.2
12	*	*		*	*						*	0.2
13	*	*	*	*	*					*	*	0.2
14	*	*	*	*	*						*	0.2
15	*	*	*			*						0.2
16	*	*	**	*	*						*	0.2
17	*	*	*							*		0.2
18	*	*	*						*			0.2
19	*	*		*						*	*	0.2
20	*	*			*						*	0.2

other authors in the literature are given in relation to the reported series.

The percentage combinations that the sesamoids most often assumed, in descending order of frequency are given in Table IV.

Worthy of but brief mention are those instances of small sesamoids that appeared in the index, long and little fingers respectively in which the lumbrical or interosseus tendons appeared to be the site of attachment. In these locations these small sesamoids appeared at the distal margin of the metacarpophangeal joint, just proximal to the base of the proximal phalanx in the area of the tendinous attachments of these muscles.

In a few cases, small osteosclerotic areas appeared in the anteroposterior view of heads of metacarpals and phalanges. Careful inspection of the lateral view showed them not to be sesamoids, but intracortical condensations. The reason for their appearance is unknown.

With the exception of the sesamoid associated with the interphalangeal joint of the thumb, the interphalangeal joints rarely have sesamoid structures.

TABLE V

PERCENTAGE DISTRIBUTION OF SESAMOID BONES IN THE FOOT

	Hallux		Hallux	2nd Toe		3rd Toe		4th Toe		5th Toe	
	T	F	IP	T	F	T	F	T	F	T	F
Males	99.7	100	14.3	2.1	0.0	0.3	0.0	0.7	0.0	9.8	0.7
Females	100	100	25.0	1.8	0.0	0.0	0.0	0.4	0.0	7.1	0.0
TOTALS	99.8	100	19.0	2.0	0.0	0.2	0.0	0.6	0.0	8.6	0.4

TABLE VI

PERCENTAGE DISTRIBUTION OF SESAMOID BONES IN THE FOOT AS REPORTED BY THESE AUTHORS

	Hallux		Hallux	2nd Toe		3rd Toe		4th Toe		5th Toe	
	T	F	IP	T	F	T	F	T	F	T	F
Burman and Lapidus[5]	100	100	13.1	3.4	0.0	0.4	0.0	0.7	0.0	16.3	2.9
Pfitzner[22]	100	100	50.6	1.6	0.0	0.0	0.0	0.0	0.0	6.2	5.5
Bizarro[2]	100	100	5.0	1.0	0.0	0.0	0.0	2.0	0.0	10.0	0.0
Kassatkin[16]	100	100	m-53.3 f-57.8	4.2	0.2	0.7	0.0	1.4	0.6	12.2	10.1

SESAMOIDS OF THE FEET

The embryology and anatomy of the sesamoids of the great toe has previously been discussed. The comparative time order appearance of ossification centers in the sesamoids of the flexor hallucis brevis as given by Francis[9] is shown in Figure 2.

In 286 male and 224 female feet, the results in Table V were obtained, with each sesamoid anatomically designated tibial or fibular for convenience.

These figures are in general agreement with those of other authors, with the exception of the interphalangeal sesamoid of the hallux. This may be due to the fact that the roentgenograms reviewed were sometimes inadequate for an accurate evaluation of the phalangeal structures. In Table VI the comparative findings of other authors in the literature are given in relation to the reported series.

Kassatkin[16] reported the observation of 5 cases in which there were sesamoids beneath each metatarsal head; a maximum of 8 in one case, distributed as follows: two beneath the heads of the first, fourth and fifth toes, and one on the medial or tibial side of the second and third toes. Other authors including Lapidus[19] and Patterson[21] report cases showing the presence of the rarer sesamoid bones. Interphalangeal sesamoids have been reported by Bizarro and Pfitzner, but their incidence is rare.

The percentage combinations that the sesamoids most often assumed, in descending order of frequency, are given in Table VII.

TABLE VII

PERCENTAGE ARRANGEMENTS OF SESAMOID COMBINATIONS OF THE FOOT IN 510 CASES

	Hallux		2nd		3rd		4th		5th		Hallux	Per Cent
	T	F	T	F	T	F	T	F	T	F	IP	
1	*	*										72.2
2	*	*									*	17.1
3	*	*							*			5.9
4	*	*							*		*	1.6
5	*	*	*						*			0.8
6	*	*					*		*			0.6
7	*	*	*									0.6
8	*	*	*						*			0.4
9	*	*								*		0.2
10	—	*										0.2
11	*	*			*							0.2
12	*	*								*	*	0.2
13	*	*	*								*	0.2

Congenital absence of the hallux sesamoids is extremely rare. In reviewing the literature only 3 cases of congenital absence of the tibial sesamoid bone of the great toe have been reported. Inge[13] reports 2 cases, and Lapidus[18] one. One case in this series of 510 feet showed congenital absence of the tibial sesamoid bone. This unusual anomaly is evidently the fourth such case to be reported and is illustrated in Figure 3. Unfortunately the roentgenogram of the opposite foot was absent.

Fig. 3. (SS 2208) White male, aged twenty-two years, eleven months. Congenital absence of tibial sesamoid of the left great toe.

In 7 instances, in the 510 feet reviewed, there were sesamoids at the tibial side of the fifth toe, and these appeared to be situated in the intrinsic musculature. This view is supported by Lapidus.[19] In 8 cases, there was present a small accessory sesa-

Fig. 4. (SS 1919) White male, aged eighteen years, eight months. Bipartition of tibial sesamoid.

Fig. 5. (SS 3519E) White male, aged eighteen years, eleven months. Bipartition of fibular sesamoid.

Fig. 6. (SS 849) White female, aged eighteen years, ten months. Bipartition of tibial and fibular sesamoids.

Fig. 8. (SS 4118B) White male, aged fourteen years. Bipartition of tibial sesamoid.

moid at the medial margin of the hallux interphalangeal joint. This was associated with a regular middle sesamoid in 3 cases and appeared alone in 5 instances.

BIPARTITION OF SESAMOIDS

Because the anatomical location of the metatarsal sesamoid bones of the great toe renders them particularly liable to trauma, it is especially important that bipartition of the sesamoids be recognized. This is of medicolegal interest, and occasionally is the basis for compensation claims. It has been shown by various authors that partition of both the tibial and fibular sesamoids does occur. Examples of bipartition of the medial or tibial sesamoid is shown in Figure 4, the fibular in Figure 5, and of both in Figures 6 and 7.

Fig. 7. (SS 2210) White male, aged twenty-one years, eleven months. Bipartition of tibial and fibular sesamoids.

Fig. 10. (SS 4118D) White male, aged sixteen years. Beginning fusion of partite centers.

Lapidus[20] demonstrated bipartition of the second toe tibial sesamoid bilaterally, and bipartition of the left third toe sesamoid. Undoubtedly others do occur.

During growth an ossicle usually appears simultaneously in each tendon. Occasionally ossification in one tendon may precede that in the other, and when this occurs the fibular usually ossifies first. In 100 boys at 15 years, Francis[9] found a double sesamoid in 26 of the tibial sesamoids, and 7 in the fibular. One boy showed a double sesamoid in each position. Of 90 girls in the 15 year age group, 27 showed division of the tibial sesamoid and only one of the fibular sesamoid.

Ossification may occur from multiple centers which may, or may not, unite subsequently. Several authors refer to failure

Fig. 9. (SS 4118C) White male, aged fifteen years. Growth of sesamoids with bipartition still present.

Fig. 11. (SS 4118E) White male, aged seventeen years. Advance of fusion of partite centers.

Fig. 12. (SS 4118F) White male, aged eighteen years. Fusion nearly complete and partition is no longer present.

Table VIII

FROM INGE AND FERGUSON, SHOWING THE DECREASE OF BIPARTITE SESAMOIDS AS AGE INCREASES, AND THE INCREASE OF FUSED CENTERS AS AGE INCREASES

Age	No. of Cases	No. of Feet Examined	No. of Feet Showing Divided Sesamoids	No. of Feet Showing Sesamoid Developed in Two Parts Now United
10	45	90	18	0
15	49	98	21	8
20	45	90	14	12
25	41	82	8	8
30	51	102	9	32
35	50	100	10	40
40	44	88	8	48
45	36	72	4	12
50	33	66	4	28
55	24	48	4	0
60+	15	30	1	28

of union of these multiple centers as congenital division. Bipartition, tripartition and quadripartition are probably better descriptive terms and are anatomically more accurate. That this is a failure of fusion is shown by the serial roentgenograms (Fig. 8 to 12) taken from the files of the Brush Foundation. It is apparent that ossification developed from two centers in the tibial sesamoid of the great toe, and, whereas bipartition can be demonstrated at 14 years, it is impossible to make that diagnosis at 18 years as fusion of the two centers has taken place.

Supporters of this contention are Inge and Ferguson[14] who showed that the incidence of bipartition of the hallux sesamoids decreased as age increased. This is shown in Table VIII taken from those authors.

In this series of 510 feet the incidence of bipartite sesamoids was carefully noted. Partitions of more than two centers have been included in the following figures. There is no statistical significant difference in the two sexes and this is shown in Table IX.

These figures are in general agreement

Table IX

PERCENTAGE OF PARTITE SESAMOIDS OF THE FEET AS TO SEX

	Hallux Sesamoids	
	Tibial	Fibular
286 males	13.6	2.8
224 females	17.9	1.8
TOTALS	15.5	2.4

Table X

PERCENTAGE OF PARTITE SESAMOIDS AS GIVEN BY THESE AUTHORS

	Hallux Sesamoids	
Author	Tibial	Fibular
Kewenter[17]	30.6	1.3
Bizarro[2]	5.0	0.0
Burman and Lapidus[5]	7.2	0.6
Powers[23]	13.0	1.0
Francis[9]	27.8	4.2

with other authors whose incidence of partite sesamoids is shown in Table x.

Kewenter,[17] in an excellent monograph, discusses the sesamoids of the big toe in 800 cases. He found no partition in 66.1 per cent of his cases; 268 cases, or 33.3 per cent, showed one division only. Of the 268 cases, 146, or 18.25 per cent, were bipartite. In 122 cases there were two or more unilateral separations. There was bilateral division of the medial sesamoid in 13.5 per cent of cases. There was division of the fibular sesamoid in 1.3 per cent of cases. This series is of the left foot alone and comparison with Kewenter cannot be made. Two of these cases showed bipartition of both the tibial and fibular sesamoids. They are shown in Figures 6 and 7.

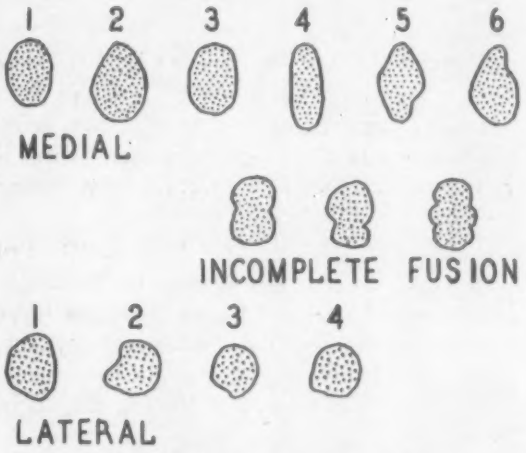

Fig. 13. (Redrawn from Kewenter.[17]) Normal sesamoids of the great toe in descending order of frequency of appearance.

The diagrams (Fig. 13 and 14) taken from Kewenter's monograph[17] show the appearance of normal and partite sesamoids of the most common forms in decending frequency of appearance.

SURGICAL CONSIDERATIONS

The surgical importance of the sesamoids has been emphasized by Bizarro,[3] Lapidus,[20] Inge and Ferguson[14] Gottlieb,[11] Sinberg,[25] Scott,[24] and others. Fracture of the great toe sesamoids is not common, and that of the thumb is rare.

The tibial sesamoid is more frequently the site of fracture than the fibular, due to the anatomical location of the tibial directly beneath the head of the first metatarsal. The fibular lies to the side and is partially protected, although several cases of fracture of the fibular sesamoid have been reported by Bizarro[3] and others.

Sinberg[25] reported a fracture of a sesamoid of the thumb in a nurse, with subsequent healing adequately demonstrated roentgenographically. Since fractures of the pollex sesamoids are extremely rare the remainder of this discussion will be related to the injury of the hallux sesamoids, although the general considerations can be readily applied to the pollex sesamoids.

Fig. 14. (Redrawn from Kewenter.[17]) Showing developmental variations of the partite sesamoids of the great toe in descending order of frequency of appearance.

Fracture of the sesamoids is usually the result of direct trauma, although a few cases appear to be due to indirect trauma. There may be associated fractures of the surrounding bones of the foot, especially of the metatarsals and phalanges if a crushing type of injury is encountered.

The differential diagnosis between fracture and trauma to partite sesamoids is important. Direct trauma to a partite sesamoid may result in ecchymosis, tenderness and pain, yet be confined wholly to soft tissue injury. Gottlieb[11] in discussing painful sesamoids states that the cause of the condition may be due to repeated "microtrauma," rather than a single severe injury. He offers as evidence the fact that most of his cases were seen in women who have worn high-heeled shoes for many years

and whose occupation called for prolonged walking or standing.

Powers[23] believes that, due to the anatomical location of the sesamoids and their developmental variations, they are frequently the seat of local pain and tenderness following injuries elsewhere in the foot.

In all suspicious injuries, roentgenograms should be made. They should be taken with the toe in marked dorsiflexion, the rays being in the frontal plane. Both feet should be examined as developmental variations are frequently bilateral.

The criteria for fracture of the sesamoids are as follows:

1. Irregular and unequal separation of the affected sesamoid with the fragments possibly being serrate.

2. Evidence or attempt at healing by the formation of callus in subsequent roentgenograms.

3. Absence of similar findings in the roentgenograms taken of the opposite side.

4. If operative removal has been done, gross and microscopic pathological evidence of fracture.

SUMMARY AND CONCLUSIONS

1. A historical, embryological and anatomical survey of the sesamoids of the hands and feet has been presented.

2. Ossification of the sesamoids of the hands and feet has been reviewed and the two year developmental lag of the male has been stressed.

3. The sesamoid structures in 529 adult hands and in 510 adult feet have been analyzed with regard to sex distribution; findings of negligible difference have been presented.

4. Partition of the sesamoids has been discussed and evidence for fusion of multiple centers has been shown.

5. A case of congenital absence of the left tibial sesamoid of the great toe is given.

6. Differential diagnosis between fracture and partition of the sesamoids is emphasized and criteria for fracture are established.

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OCCUPATIONAL CALCAREOUS PERITENDINITIS OF THE FEET

A CASE REPORT

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THE purpose of this paper is to present an unusual case of calcareous peritendinitis of the peroneal tendons of both feet. An attempt will be made to evaluate the findings in the light of the patient's occupation.

It is believed that no similar case has been previously reported in the literature. Roberts,[3] reporting 50 cases of bursitis of the foot in 1929, mentions only the head and base of the fifth metatarsal as sites for the formation of adventitious bursae on the outer aspect of the foot. However, such bursae may conceivably occur at any point along the outer aspect of the foot where pressure and friction are constantly applied. Inflammatory and degenerative changes may lead eventually to the deposition of calcium salts in the wall of the bursa, in the adjoining tendon sheath, or in the tendon itself—the pathological mechanism being similar to that so commonly seen in the bursae and tendon cuff of the shoulder.[2]

CASE REPORT

G. G., male, white, aged thirty, house-painter, awoke on the morning of December 1, 1946, with pain over the outer aspect of his left foot. The pain rapidly became quite severe, and he consulted his doctor, who sent him to the

FIG. 1. Left foot, showing the original appearance of the calcification on the lateral aspect of the calcaneocuboid articulation.

Fig. 2. Right foot, showing a similar calcified deposit.

Newton-Wellesley Hospital for a roentgen examination of his left foot (Fig. 1), which revealed a fragmented calcific deposit just lateral to the calcaneocuboid articulation. This unusual finding prompted examination of the other foot, which showed an almost identical calcified mass (Fig. 2). The patient was unable to bear any weight on his left foot, and the involved area was hot and swollen. His doctor strapped his foot and prescribed rest, and the pain and swelling subsided somewhat. A week later, however, the same symptoms appeared with greater severity in the other foot, and he was admitted to the Cushing Veterans Administration Hospital.

The general physical examination was essentially negative. The temperature, pulse and respiration were normal. In the right foot there was extreme tenderness over the lateral aspect of the cuboid. The skin was red and the tissues slightly edematous. In the left foot, definite point tenderness was elicited over the lateral aspect of the cuboid. The laboratory findings were normal, with the exception of the sedimentation rate, which was raised to 29 mm.

Fig. 3. Appearance of the calcified deposits four weeks following operation on the right foot. The calcification is seen to follow the course of the peroneal tendon sheath; this is particularly evident in the left foot.

(normal 8–10 mm., Wintrobe); this returned to normal in a week.

On December 19, under local anesthesia, a No. 21 gauge needle was passed into the sheath of the peroneus longus and brevis over the calcaneocuboid articulation of the right foot. The sheath was infiltrated with novocaine, and the needle was then passed beneath the sheath toward the cuboid. In this area a grating sensation was transmitted from the tip of the needle. Two or three drops of material, white in color and of the consistency of toothpaste, were obtained from this area, which was then approached with needles of varying gauge. No successful irrigation was carried out, and no further material could be obtained. Culture of the aspirated material produced no growth in seventy-two hours.

Two weeks later the patient was asymptomatic except for slight tenderness over the lateral aspects of both feet in the region of the cuboids. Roentgen examination about this time showed that the calcification was distributed along the course of the peroneal tendon sheath on both sides, though there was a marked reduction in the total amount present, particularly in the right foot (Fig. 3).

The patient was discharged six weeks after admission, apparently cured. He was seen again at the Newton-Wellesley Hospital in August, 1947. Roentgen examination at this time showed only a few tiny flecks of residual calcification near both cuboids (Fig. 4). The anterior surfaces of the tibiae showed no essential variation from the normal. (This latter examination was made at the suggestion of Dr. Merrill C. Sosman, who has noted proliferative changes in the periosteum of the anterior surfaces of the tibiae in house-painters, due to the pressure of the lower legs against the ladder rung.)

Fig. 4. Eight months later the calcification is barely visible as a few tiny flecks near each cuboid.

The occupational aspects of this condition were closely investigated by careful questioning of the patient. For nine years of his life, from 1935 to 1944, he had spent an average of at least four hours a day on ladders of the long narrow-runged type. From 1944 till his discharge from the Army in March, 1946, he had not been engaged in this type of work. Between March, 1946, and the onset of his illness his jobs had involved ladder-climbing on only two occasions, the last being just two days prior to the acute episode. On that day he had spent eight hours working on a ladder. At no time in the past had he ever experienced pain of a similar nature in his feet.

The patient was asked to simulate his accustomed stance while working on a ladder,

using as a convenient model the side-bar between the legs of a chair. It was found that, as he braced himself against the legs of the chair, the point of pressure corresponded exactly to the original areas of tenderness and calcification.

The patient has had no recurrence up to this date, and has pursued his work in a normal manner—though he has been careful to refrain from working on ladders.

DISCUSSION

Anatomy (Fig. 5). The tendons of the peroneus longus and brevis muscles are invested by a common synovial sheath which begins at the back of the external malleolus and divides as it approaches the peroneal tubercle of the calcaneum. The upper portion is prolonged on the peroneus brevis tendon almost to its insertion at the base of the fifth metatarsal; the lower portion ensheaths the peroneus longus (with or without interruption at the lateral side of the foot) across the sole of the foot to its insertion in the first cuneiform and base of the first metatarsal.[1] These tendons are the chief evertors, and the tendon of the peroneus longus moreover forms a most important sling in the middle of the arch of the foot.

When standing on the rung of a ladder, the average person automatically balances himself by bracing his feet against the sides of the ladder, so that the point of pressure on the lateral aspect of the foot coincides with the cuboid tuberosity over which the peroneal tendons pass. The tendons are thus pressed closely up against a bony prominence during the very time that they are being stretched by the synergic action of the peroneal muscles, which are, in conjunction with the invertors of the foot, operating to maintain a constant balance. It is believed that this unusual occurrence of pressure by two unyielding surfaces on a tendon relatively immobilized by its functional tautness offers a reasonable explanation for the development of the condition described in this paper. It must be assumed that bruising and irritation of the soft tissues was followed in the course of time by a localized degeneration and the deposition of calcium salts. The tendons and tendon sheaths have a lining membrane similar to the synovial membrane of joints

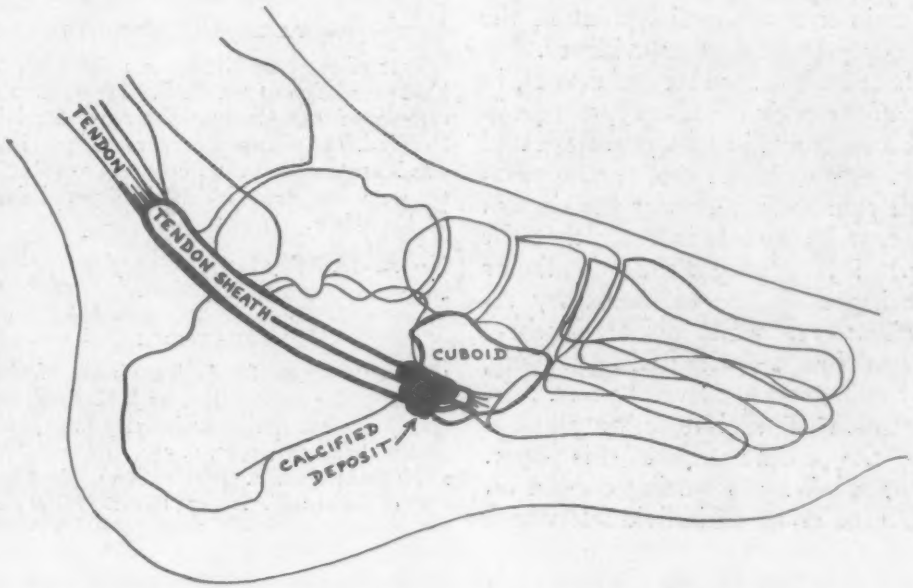

Fig. 5. A tracing made from Figure 1 to show the relation of the calcification to the peroneal tendon sheath.

and bursae, and it is well known that post-traumatic degeneration of this specialized tissue is frequently followed by calcification in the subsynovial tissue strata.

From an anatomical point of view, it must be admitted that there are three areas where the calcification may have occurred in this particular case: in the tendon itself, in the tendon sheath, or in the wall of an adventitious bursa formed between the tendon sheath and the cuboid. The course of the calcification as seen in Figure 3 tends to rule out the last possibility, but the exact anatomical location must remain a controversial point in the light of our present meager evidence.

The most logical sequence of events, in the light of the patient's history, can probably be reconstructed as follows: Repeated slight trauma over a period of several years led to the calcification seen at the time of the first examination. It is likely that the sudden new injury was the causative factor in producing the acute inflammatory response which occurred in the areas where the large calcium deposits had been lying, relatively quiescent, for several years. Further discussion of this interesting problem is beyond the present scope of this paper. An investigation is now being carried on among a large group of individuals whose occupation necessitates work of the same nature as that engaged in by the patient in this case history. These findings will be reported at a later date.

SUMMARY

(1) An unusual case of calcareous peritendinitis of the peroneal tendons of both feet is presented.

(2) It is suggested that this is an occupational disease which has not been previously reported as such, and which may possibly occur more frequently than is realized in house-painters and in those who spend a great deal of their time on narrow-runged ladders.

ACKNOWLEDGMENTS

Part of the case history was obtained, with the kind permission of Dr. R. E. Carroll, from the case records of the Cushing Veterans Administration Hospital. The roentgenogram reproduced in Figure 3 was borrowed from the Department of Radiology of the same hospital, with the kind permission of Dr. D. Kornblum.

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KAPOSI'S SARCOMA

REPORT OF TWO CASES*

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KAPOSI'S sarcoma, or multiple idiopathic hemorrhagic sarcoma, is an unusual disease among adults in America. Two cases are presented that represent the acute fulminating and the chronic aspects of the disease.

REPORT OF CASES

CASE 1. F. McG., an American born white male, aged fifty-eight, with a twelve year history of skin lesions.

The disease began seven years prior to the first admission, August 3, 1942, when a small red area developed on the nose. Since, similar lesions have appeared on the right foot and left ankle. On examination there were numerous papillary growths, dark in color, with other areas of blue demarcation.

The patient was referred to the X-ray Therapy Department for treatment of the lesions of the medial surface of the right foot, the left ankle, lower left leg and a developing lesion of the sole of the right foot. Over a two month period he received 3,840 r to the lesions of the right foot and 3,200 r to those of the left ankle. Additional therapy was given to the sole of the right foot and to the original right foot area and a recurrence at the base of the fourth right toe. A total of 12,000 r, measured in air, was given to the lesions of the feet and ankles with a poor response to the irradiation.

In June, 1943, the patient was again admitted complaining of swelling in the throat of four to five months' duration which caused difficulty in swallowing, and nausea. During the past eight years a gradual loss of 17 pounds had occurred. No other symptoms referable to the gastrointestinal tract were present. There was an additional lesion on the penis just above the coronal sulcus. An irregular blue-red mass was removed from the anterior surface of the uvula. Microscopically, the specimen revealed the connective tissue to be infiltrated by a very vascular tissue, the cells of which were mainly spindle shaped with elongated dark staining nuclei. Numerous thick-walled small blood vessels were noted with intimal proliferation and some ecchymosis into the tissue and under the epithelium of the mucosa. Diagnosis: Multiple hemorrhagic sarcoma.

The third admission, May, 1944, was for marked swelling of the right leg to the knee and secondary infection. After treatment with warm saline soaks, elevation of the leg and sulfadiazine by mouth, a mid-thigh guillotine amputation was performed. Microscopically the sections revealed a fibroblastic growth in the subcutaneous tissues with cells of the oat cell variety with long thin nuclei and interweaving among themselves in a true sarcomatous arrangement. The tumor was quite vascular and in places was almost mesh-like from the number of small blood vessels present. Diagnosis: Kaposi's sarcoma.

FIG. 1. Case 1. Lesion of the sole of the right foot.

The last admission, January, 1945, was for treatment of a secondarily infected tumor of the left third toe. Since the amputation of the right leg, the patient had gained 20 pounds in weight and had no symptoms referable to the gastrointestinal tract.

When the patient was last seen in February, 1947, there were extensive lesions of the left ankle and foot, of either arm and one small reddened area of the amputation stump. He had slowly lost weight but otherwise his condition was fairly satisfactory and his hemoglobin

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Fig. 2. Case I. Lesions of the left foot and lower leg.

and red blood cell count remained within normal limits throughout the disease.

Case II. G. M., an Italian born, white male, aged fifty-seven, with an eight month history of the disease.

Fig. 3. Case II. Original lesion of the tonsillar area.

In July, 1946, he began to have difficulty in swallowing and was seen by several physicians who gave him various treatments for a tumor-like mass of his throat. One removed a small tumor from the tonsillar area which bled considerably during and after the operation.

A large sessile tumor was removed from the left tonsillar area in November, 1946. Complete examination of the throat at that time revealed

Fig. 4. Case II. Tumor mass removed from the tonsillar area.

multiple bluish hemorrhagic lesions filling the vallecula and the base of the epiglottis. The palm of the left hand also had bluish hemorrhagic lesions and the dorsum was edematous. It was believed that the swelling of the hand was due to a mass in the supraclavicular and axillary areas. Large inguinal nodes were present with considerable edema of the feet and legs.

The patient was given roentgen therapy over the supraclavicular and axillary areas resulting in slight reduction in the size of these nodes and improvement in the swelling of the left hand.

Shortly after the completion of the roentgen therapy, the patient began to complain of nausea and almost constant abdominal pain.

He passed several tarry stools. A marked anemia was present with a hemoglobin of 40 per cent. A gastrointestinal series on December 19, 1946, showed multiple papillary or polypoid lesions of the small intestine.

The patient has continued to have gastrointestinal bleeding and has received six transfusions during the past two months. The hemoglobin has continued to remain about 50 per cent. During this period he has received daily treatments with varying dosages of mustard gas with little or no response.

Fig. 5. Case II. Lesions of the palm of the left hand.

When last seen during the second week in February, 1947, the patient's condition had rapidly become worse. He continues to have gastrointestinal bleeding. Enlargement of the liver with the development of ascites had occurred.

This interesting condition was first described by Kaposi in 1872, who found histopathologically a small cell sarcoma. He thought it was a general disease because it began at the same time on both the hands and feet.[8]

The disease is one of geographic rather than racial incidence, chiefly affecting the inhabitants of central and southeastern Europe. It is common in northern Italy Russia, Poland, and "is relatively common in New York City and other cosmopolitan urban centers."[10] The highest incidence is in the age groups fifty to seventy and is rare in children "less than one percent of the reported cases occurring under the age of ten years."[1] It is uncommon in Negroes. The

Fig. 6. Case II. Lesions on the dorsum of the left hand.

condition is about twenty times more common in males than females.

The etiology is unknown. One group believes that the condition is a true neoplasm and the other that it is an infectious granuloma. Investigations were done by Choisser and Ramsey[2] based on the proposition that "if the disease were of infectious origin it should be possible to isolate the causative organism from the lesions, to cultivate it and to transmit the disease to experimental animals." These writers came to the conclusion that Kaposi's sarcoma is in all "probability a true neoplasm derived from the reticulo-endothelial system and is best described by the term angio-reticulo-endothelioma."

The disease is usually first manifested by skin lesions but cases have been reported in which visceral lesions have preceded the cutaneous manifestations. The lesion usually begins as a reddened macular area on an extremity, most commonly the leg or foot. As the lesion ages it becomes firm, the color gradually becomes bluish and the macules develop into varying sized papules. These changes are easily understood by a comparison of the microscopic appearance of the lesion in its various stages. At first the parenchyma is infiltrated and compressed by a new formation consisting of new blood vessels and a richly cellular connective tissue. There is an increase of the reticulum as demonstrated by the Bielschowsky stain. The reticulum is closely

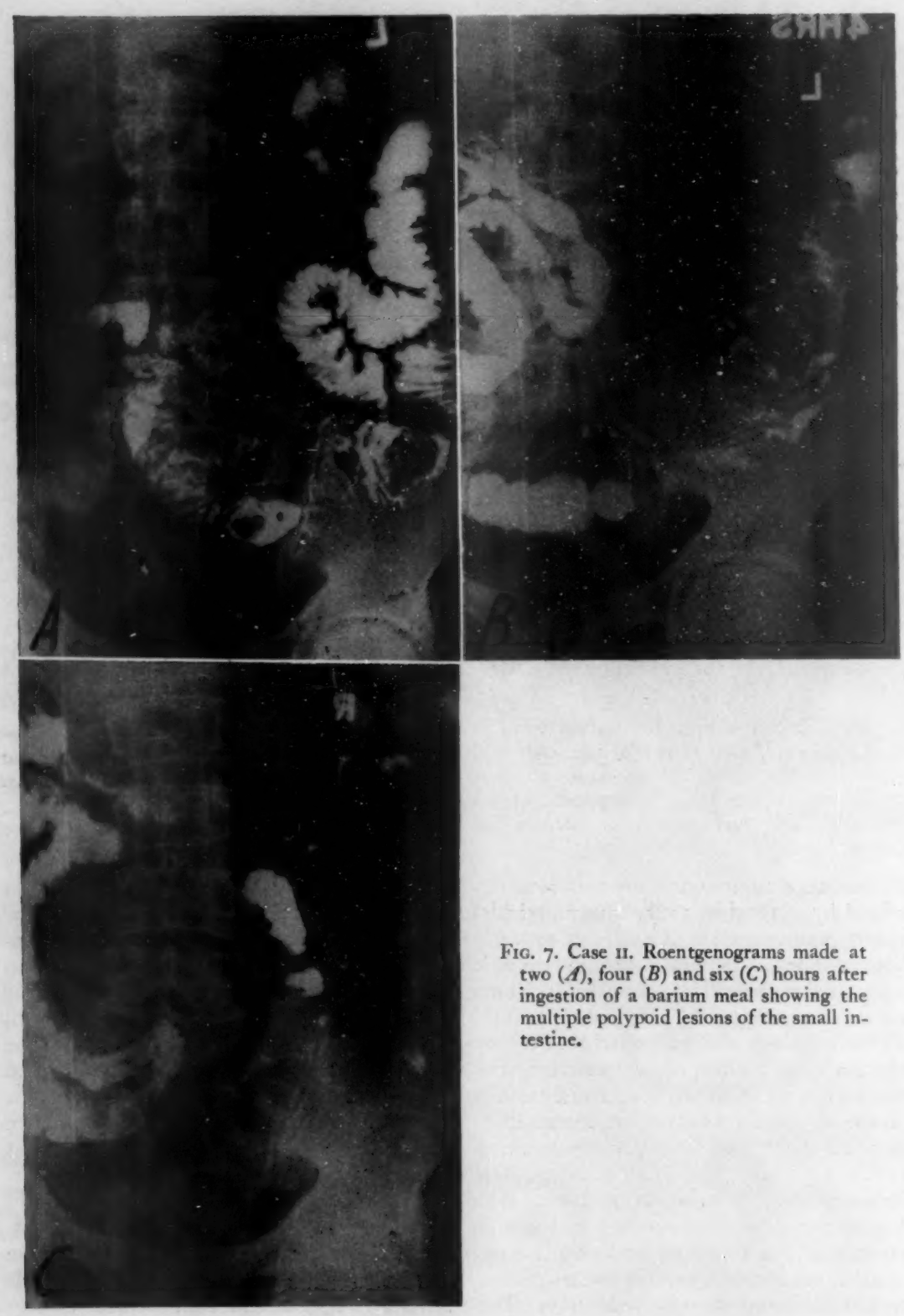

FIG. 7. Case II. Roentgenograms made at two (*A*), four (*B*) and six (*C*) hours after ingestion of a barium meal showing the multiple polypoid lesions of the small intestine.

associated with new vessels and precedes them in invading partially destroyed parenchyma. As the lesion ages the cellular elements increase and there is stagnation of the blood, and hemorrhage into the surrounding tissues. The endothelial cells seem to change into a fibroblastic type of cell and a marked increase of a richly cellular tissue with large oval or spindle nuclei resembling a young connective tissue is seen. The acute cases show more malignancy in individual cell structure as evidenced by pleomorphism, hyperchromatism, abundance of mitotic figures and embryonic cell types.

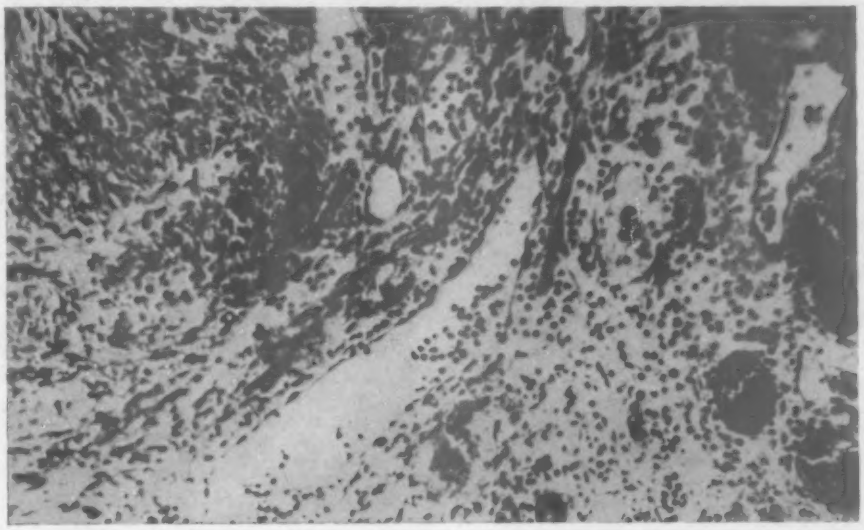

Fig. 8. Photomicrograph of early stage demonstrating rich vascularity, spindle and round cells of the tumor.

Autopsy findings reveal that nearly every organ of the body may be involved by the disease. Lesions in the muscles, though rare, have been reported, particularly in the diaphragm and the intercostal muscles. No lesions have been found in the substance of the brain or spinal cord, but "the dura supposedly has been involved in one reported case."[4]

Ordinarily the course of Kaposi's sarcoma is slow and steadily or intermittently progressive. Old lesions often undergo spontaneous involution. The extent is from eight months to twenty-five years with the average duration being between five and ten years. Death usually occurs from intercurrent infection or infiltration of the lungs, spleen or liver, but the most common occurrence is metastasis to the intestinal mucosa with ulceration and hemorrhage.

Practically all authorities agree that roentgen therapy probably gives the best results in treatment of the disease, but this is palliative. It is the early vascular lesion that usually responds to small doses of low voltage roentgen therapy, while the later type of lesion is much more resistant to treatment. Most of the lesions can be made to disappear with moderately heavy radiation dosage. However, if the patient is young, with a life expectancy of ten to fifteen years, irradiation has not proved to be a very satisfactory method for control of the disease.

The use of radium and radon therapy is not satisfactory because of the numerous lesions and the large areas that have to be treated.

Arsenic has been used either alone or in conjunction with roentgen therapy. It has been administered chiefly by mouth as Fowler's solution, but has been given

Fig. 9. Photomicrograph of late stage lesion in the dermis revealing compact arrangement of spindle cells and decreased vascularity.

parenterally as well. When used, the treatment should be intensive.

Other methods of treatment which are seldom used are surgery, electrodesiccation and electrocoagulation. Modified mustard gas and the nitrogen mustards are relatively new and their effects have not been proved.

Forman[6] reported a case that showed spontaneous healing.

MacKee and Cipollaro[10] believe "that recurrence, sooner or later, is the rule, and that, while the treatment agent causes involution of the eruption to which it is applied, it has little or no influence on the etiology of the disease and it does not prevent the development of new lesions in various parts of the body."

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RADIUM THERAPY FOR CARCINOMA OF BARTHOLIN'S GLANDS*

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CARCINOMA of Bartholin's glands (greater vestibular glands) is rare and a poor prognosis is justified should the capsule be perforated by the malignant process. The purpose of this paper is twofold: to note the cases of carcinoma of Bartholin's gland represented in the surgical records of the Mayo Clinic, and to record that judicious radium therapy and roentgen therapy, either or both, are indicated as curative procedures, even after local recurrence and clinical metastasis.

Between January, 1910 and December 31, 1947 inclusive, approximately 700 benign lesions of Bartholin's glands were surgically treated and microscopically studied at the Mayo Clinic: this number included cysts, abscesses and chronic inflammatory conditions. During the same period, 7 primary malignant growths of this gland were found, or an incidence of 1 per cent of all lesions of Bartholin's glands for which operation was performed, which compares closely with the 1.1 per cent quoted by the New York Post-Graduate Hospital group.[28]

Rabson and Meeker quoted Lynch and Maxwell concerning the general frequency of carcinoma of Bartholin's glands: "this tumor is undoubtedly rare, yet the literature does not properly express the frequency, since vulval growths are usually seen by the men in general practice who do not report them and who may be content merely with their removal." It is realized that in a case of squamous-cell carcinoma of Bartholin's gland in which the vulva is infiltrated and the condition has been neglected, the origin of the malignancy cannot be stated. Vulval malignancy is not uncommon.[7] Moore stated that it ranks third among neoplasms of the female genitalia. It may involve Bartholin's gland by direct extension. This eventuality needs to be excluded when referring to true carcinoma of Bartholin's gland.

Spencer listed 13 cases from the world literature, and reported 1 additional case. Falls listed 16 cases from the world literature, and stated that the first report by a resident of the United States of a case which occurred in that country appeared in Kelly's "Operative Gynecology" of 1907, page 253. Falls added a report of 1 case. Rabinovitch estimated the world literature to contain reports of 40 cases and added a report of 1 case. Harer found reports of 30 cases, some of which he considered doubtful. Lyle found reports of 36 cases, 11 from the United States, and reported 1 additional case. Rabson amd Meeker found reports of 56 cases and added 2. Simendinger listed 38 cases from the world literature and added a report of 1 case. Taussig mentioned 9 cases of carcinoma of Bartholin's glands among 155 cases of vulval carcinoma, but gave no detail specifically concerning these cases. Pund and Cole added a report of 1 case. Boughton estimated that the world literature contains about 75 reports of cases, many of which were published with insufficient data. She added a report of 1 case. Hynes reported 1 case. LeDoux stated that 2 cases are on record at Hotel Dieu, New Orleans, and added a report of 1 case which he had observed in twenty-five years of experience. Crossen

* Abridgment of paper presented at the Thirtieth Annual Meeting of the American Radium Society, Chicago, Ill., June 20–22, 1948.

stated that 88 cases have been reported in the world literature. He reported 1 additional case.

We can therefore estimate from available world literature that between 50 and 90 cases of carcinoma of Bartholin's glands have been reported, including recent reports from the foreign literature.[1,2,6,21,25,34] The number varies according to the rigidity of the criteria which one chooses to apply to the cases.

The normal embryology and histology of Bartholin's glands are perceptible in the female embryo of nine weeks. The glands appear as paired, solid, epithelial outgrowths from the vestibular epithelium of the urogenital sinus.[3,16,28]

In the female adult each gland measures 2 by 13 mm. The glands lie on the urogenital diaphragm in the paravaginal tissue, surrounded by the vascular vestibular bulb, being separated from the vagina by the bundles of the vaginal sphincter and part of the perineal soft tissues. The chief excretory duct lies within 1 to 2 mm. of the border of the labium minus, with its lumen opening into the vestibule just below the border of the hymen (1 cm. above the fourchet). The gland is well encapsulated. Cullen described the arrangement of the gland as follows: "The entire gland may be likened to a bunch of grapes, developed more on the one side than on the other. The main duct corresponds to the stem; the secondary and terminal ducts to the branches, and the lobules represent the individual grapes."

Bartholin's gland is a mucus-secreting gland of tubulo-alveolar character.[22] The normal histologic picture is unique and is not simulated by any other glandular structure of the labia.[4] The terminal excretory ducts are lined with one to several layers of cells that are cuboidal to columnar in charter, and unite into an ampulla lined by columnar epithelium. The true excretory duct is lined with flattened transitional or vestibular squamous epithelium.[28]

As with carcinoma in general, the etiology of carcinoma of Bartholin's glands is obscure. The role of chronic inflammation, previously thought of etiologic importance, is probably not noteworthy. More than half of the patients whose cases have been reported have been more than fifty years of age; the condition has been reported to have afflicted unmarried women, but never as yet a virgin.[13]

The early diagnosis of malignancy of Bartholin's glands is made probably less frequently than that of malignancy of any other organ of the body.[27] This would not be true if all "cysts or abscesses" of this gland were made the subject of careful pathologic study.[4]

Carcinoma of Bartholin's gland is first noted as a small, hard, painless, nodular swelling lying deep in the posterior portion of the labial fat, movable at first but months or years later becoming fixed to surrounding tissue. Then pain develops and commonly is referred to the coccyx or rectum. Because of the associated vulval edema, this pain is exaggerated by menstruation or coitus. After a variable interval, parts of the growth become necrotic and semifluctuant and, when overlying skin is destroyed, the tumor becomes infected, giving rise to a chronically discharging sinus. The malignancy tends to invade deeply to involve surrounding fat and muscle, and later the pubic bones. The inguinal lymph nodes are enlarged in more than 50 per cent of cases, either by metastatic involvement or secondary to vulval necrosis and infection.

Histopathologically, these tumors have features of architectural arrangement and cytologic detail in common with the epithelium of Bartholin's glands and ordinarily the growths can be recognized as having arisen from that gland.[27] Because of the two different kinds of epithelium found in Bartholin's glands, it is not surprising to find here two histopathologically different growths: adenocarcinoma (columnar) and squamous-cell carcinoma, both analogous to neoplasms of the uterine cervix.[27] Adeno-

carcinomatous types predominate over squamous-cell types in the proportion of 2.5 to 1.[28,31]

Rabson and Meeker quoted J. H. Honan (Ueber die Carcinome der Glandulae Bartholini, Inaugural Dissertation, Berlin, 1897) as enumerating four criteria before an indisputable diagnosis of primary carcinoma of Bartholin's gland can be made: (1) typical vulval site, (2) position deep in the labium, (3) connection with the duct of the gland and (4) presence of intact glandular tissue. If, in addition to the above, the skin is intact and the malignancy is adenocarcinomatous in type, the greater vestibular gland is unquestionably the primary site. However, it should be remembered, as noted by McDonald and others,[19,20] that vulval sweat glands can give origin to adenocarcinoma. Other adenomatous structures, which rarely present in the vulva, and which even more rarely become malignant, are accessory breast tissue and remnants of the wolffian duct system.

With respect to squamous-cell carcinoma, the problem of primary site is not readily clarified because the patient may neglect examination until the adjacent vulva is grossly involved, at which time the site of origin is lost. However, in early cases the point of origin can be more easily ascertained. If, on histopathologic study, normal glandular structure lined by columnar epithelium is seen contiguous to the squamous-cell malignant growth, it is assumed that the origin is the stratified squamous epithelium which normally lines the main excretory duct or that the normal columnar and transitional cells of the deeper portion of the duct system have undergone metaplasia to squamous cells, such as occurs in the presence of chronic infection of Bartholin's glands.[32]

In differential diagnosis, it is necessary to consider primary tuberculosis of Bartholin's glands, of which 3 cases have been reported, syphilis, which rarely attacks these glands, and sarcoma, which is extremely rare in this anatomic region.[35] Infection of Bartholin's glands, gonorrhea for instance, is usually bilateral and tends to regress with treatment.

In general, the prognosis of malignancy of Bartholin's glands is poor, the most important factor in the poor prognosis being failure to make early diagnosis. Boughton expressed the belief that malignancy here is curable if excision is done before the capsule has been invaded. In most reports of cases, the final outcome is not stated. Falls quoted Trotta (*Arch. di ost. e gin.*, 1900, p. 193) as reporting the only six-year cure up to the period of his (Falls') report. Lyle mentioned 3 cases of recurrent adenocarcinoma of Bartholin's gland (from Dr. W. P. Healy's files), in all of which operation previously had been performed for supposedly benign lesions, and in all of which the patients were well four or five years after the most recent operation. Rabson and Meeker, after communication with Mayo and Barber, and with Lyle, regarding survival of patients who previously had been the subject of report by these latter authors, stated that 2 patients were alive eleven years after the original operation. Rabson and Meeker also noted that the longest survival after surgical operation which had not been supplemented by radiotherapy was three and a half years. Simendinger stated that of 21 cases concerning which information on recurrence was available, there was no recurrence in 1 case after six years, in 1 case after four years, in 5 cases after two years, and in 4 cases after one year. Taussig noted that 3 patients with carcinoma of Bartholin's glands were alive five years after treatment. Hynes recorded that 1 patient was clinically well three and a half years after radical excision with cautery. LeDoux's patient who had a squamous-cell carcinoma, grade 3, of Bartholin's gland, had survived seven years, to the time of LeDoux's writing, with no recurrence, after radical excision and postoperative application of radium.

Lyle expressed the belief that malignant growths of Bartholin's glands should be

treated as vulval carcinoma; namely, by primary wide excision of the vulva, followed by secondary dissection of the inguinal and femoral lymph nodes. He gave as his opinion that local and regional irradiation are of value. Taussig's and Folsome's view agree with the one just expressed except that both of the latter expressed the belief that preoperative and postoperative irradiation are of no value.

Most authors have set down the belief that carcinoma of Bartholin's glands metastasizes by way of the lymphatic structures as does vulval carcinoma. Taussig described the lymphatic drainage from the vulva as passing chiefly through the inguinofemoral nodes of both sides, and less extensively through the external iliac, obturator, hypogastric and ureteral lymphatic chains. Since special study of the lymphatic drainage of Bartholin's glands has not been undertaken, Boughton expressed the belief that the application of conceptions of vulval lymphatic drainage in treatment of malignancy of Bartholin's glands is open to question, especially if the carcinoma under consideration is believed to have arisen in the deeper portions of a gland. It is interesting to note that Rabson and Meeker's patient, accidentally killed nine months after surgical operation and irradiation, was found to have extensive metastatic growths in the brain, dura, lungs, heart, liver and so on, with no evidence of local recurrence; such widespread metastasis suggests spread via the blood stream.

Cowper's glands (the bulbo-urethral glands) should be of collateral interest in this study. They are the male homologues of Bartholin's glands. The organic similarity of structure of the two sets of glands has been described by Schaffer. Cowper's glands are two small, round or oval structures lying in the urogenital floor, between the two layers of the median perineal aponeurosis, and between the deep surface of the membranous urethra, at the level of of the triangular ligament, and the apex of the prostate gland. They are of mucous, tubulo-alveolar structure and their alveoli are lined with low columnar cells; mucus-secreting elements are present in great numbers.[12] Only 6 cases of primary malignant tumor of Cowper's glands have been reported in the literature; all were adenocarcinomas with structure suggesting cylindroma. Chief complaints were of rectal pain, mass in the perineum and urinary disturbances. Treatment has been perineal cowperectomy followed by implantation of radon and use of roentgen therapy. Routine rectal examination is the most important method of arriving at a correct preoperative diagnosis.

REPORT OF CASES

Case 1 (previously reported by Hunt and Powell and Mayo and Barber). This patient was married and had had 1 child. She was thirty-seven years of age when she registered September 26, 1924. Four years before, she had noted a cystic tumor in the vulva. The tumor had enlarged very slowly except for the past year, when, she thought, the rate of growth had increased. Examination revealed a nonulcerated, solid tumor in the region of the left Bartholin gland and enlarged right inguinal lymph nodes. At operation, September 30, 1924, the tumor was excised. The sphincter muscle of the anus was infiltrated and in all likelihood all of the tumor was not removed. The pathologist's report read: "Adenocarcinoma grade 2 of Bartholin's gland (5 by 4 cm.)."

Postoperative radium therapy was outlined October 31, 1924. The operative wound was healed. The inguinal nodes on the right were finely nodular and enlarged.

An American-type tube, the wall of which consisted of 0.5 mm. silver, and which contained 50 mg. of radium sulfate (element), was placed in a vaginal applicator. Filtration was through an additional 1 mm. of brass and 2 mm. of hard rubber. The outside diameter of the apparatus was 1.5 cm. and the length, 4 cm. One applicator was applied at a time to each of three fields: the operative site, the middle vaginal segment and the low vaginal segment. Each applicator remained in place for fourteen hours. The areas over the right and over the left inguinal lymph nodes, and the vulval area, were mapped out in small fields measuring about 4 by 4 cm. There was a total of six fields in each groin area and of four fields in the vulval area.

The applicator was a balsa wood block, of which the base measured 3 by 4 cm. and the thickness was 2.5 cm. To this block one American-type tube, of the sort previously described, was attached and filtration through an additional 2 mm. of lead and through an additional 2 mm. of rubber was provided. Three of these blocks were applied at a time, first to the right and next to the left groin. Some of the exposures were for fourteen and some for twenty hours. Two of these blocks were applied at a time to the vulval fields and were left in place for fourteen hours each.

The patient returned many times for reexamination. Naturally, the data that follow will be only a portion of the record.

She returned February 4, 1931, stating that for the past ten days a nodule had been present at the site of the old operation. Two days later the tumor and scar tissue were excised. The pathologist's report read: "Adenocarcinoma, grade 2."

Between February 11, 1931, and May 20, 1932, the patient received colloidal lead phosphate intravenously.

She returned April 26, 1933. At this time the scar tissue in the primary site was very firm and abundant. However, a small, oval infiltration in one of the heavy strands of scar tissue could be palpated. Punch biopsy was done. A pathologist's report read: "Adenocarcinoma, grade 1." There was a nodular infiltration measuring 1 by 1.5 cm., low in the pole of the right labium majus. Two platinum-iridium needles, each containing 1 mg. of radium sulfate (element) and the walls of which were 0.4 mm. thick, the diameter of each, 1.25 mm., and the total length of each, 10.0 mm., were placed in the substance of the oval infiltration and six needles were placed in the tumor that had been found in the labium majus; all of these eight needles were left in place for forty-eight hours.

The patient reported again January 15, 1934. At this time there was a small region of infiltration in the fourchet (right posterior). Biopsy resulted in a report of adenocarcinoma, grade 1. Nine of the needles previously described were placed in the region of involvement and were left there for forty-eight hours.

When the woman returned on September 11, 1934, there was definite subcutaneous infiltration, 1.5 cm. in diameter, in the left perineal region, near the anal wall. Punch biopsy was done and the pathologist's report read: "Adenocarcinoma, grade 1." Five of the needles previously described were placed in this region and were left in place for forty-eight hours.

At the patient's revisit, January 15, 1935, infiltration on the left side, very near the external urinary meatus, was found. Seventeen needles of the kind previously described were placed in this area and in the adjacent left labium majus, where they were left for twelve hours.

On August 18, 1936, the patient visited us again. The infiltration in the old treatment field, low in the right labium majus, seemed to have increased in size. There was a cutaneous infiltration near the anus on the right side, 0.5 cm. in diameter. Fifteen needles of the type previously described were distributed in these regions of activity and remained in place for forty-eight hours.

Again the woman returned, December 8, 1936. She complained of pain in the right hip and that this pain extended down the upper part of the right thigh. Roentgenograms of the right hip revealed metastasis to the neck and trochanteric region of the femur. Roentgen therapy was employed as follows: 200 kv., distance 50 cm., 15 ma., filtration 0.75 mm. copper and 1.0 mm. aluminum, time 30 minutes each to two large anterior and two large posterior fields in the region of the head of the femur. Subsequent examinations proved the treatment to have been effective.

On October 11, 1943, when the patient was seen again, extensive malignant activity was present in the primary field and in other vulval and perineal regions. Micturition and defecation were painful and difficult. The inguinal lymph nodes were bilaterally enlarged. The inguinal areas were mapped out in four small fields on each side and the small, balsa wood block applicators, previously described, were applied four at a time and were left in place for fourteen hours each. The vulval area and the perineal area were taken together and divided into two large fields, each about 7 cm. square. To each of these fields a balsa wood block which measured about 7 cm. square at the base and which was 5 cm. thick was applied. On the upper surface of each block were four American-type tubes, previously described, and filtration through an additional 2 mm. of lead was provided. The blocks were left in place, on one area at a time for twenty hours.

When the patient returned, January 20,

1944, she had only fair control of urine and feces. Activity included the vulval and perineal regions. The orifices of the vagina, urethra and anus could not be identified. Radium was applied by limited contact to selected fields of the above regions. Four American-type tubes, of the sort previously described, contained in rubber tubing of which the wall was 2 mm. thick, were strapped together with adhesive plaster, forming a surface applicator; application was for three and a half hours to each of six areas.

At the revisit of June 21, 1944, urinary distress, especially nocturia, urgency, frequency, and slight loss of control were the woman's chief complaints. There was definite activity in the old treatment fields. The pubic, vulval and anal areas were mapped out in four small fields each and four small block applicators, previously described, were applied, four at a time to each area but to only one area at a time, for twelve hours.

On September 29, 1944, when the patient returned again, she was hospitalized on account of vesical stones. The urethra was dilated easily to a size of 29 F. Two calculi were found in the bladder; litholapaxy was done and the fragments evacuated. The radium therapy carried out at the last previous visit was repeated.

On account of urinary retention, the woman returned April 15, 1945. Under general anesthesia, the scarred urethra was located and dilated to a size of 28 F. The bladder contained 2,000 cc. of urine. The vesical mucosa was markedly hemorrhagic. A No. 24 irrigating catheter was put in place.

The last admission of the patient to the hospital was September 23, 1946, for nursing care. The course was slowly retrogressive. On account of metastasis to the cervical portion of the spinal column, and to effect relief of pain, roentgen therapy was given December 30, 1946, using the following factors: 130 kv., distance 16 inches, 6 ma., filtration 5 mm. aluminum, time 17 minutes to each of four fields, two anterior and two posterior to the left shoulder. The same treatment factors were employed January 14, 1947, for further palliation.

Death occurred January 24, 1947. At necropsy the carcinoma was found to have extended to the liver, lungs, ribs, spinal column, cecum and so forth. Ulceration of the perineum, destruction of the anal sphincter, chronic cystitis, subacute ureteritis, pyelitis, bilateral pyonephrosis and hydronephrosis also were noted.

Comment on Case I. The patient survived twenty-six years after onset of the disease. At the time of the operation the primary lesion invaded the anal sphincter and was only partially excised. The inguinal lymph nodes were enlarged. Radium therapy in the beginning was designed for cure but later was applied in a limited way because palliation was all that could be expected. Roentgen therapy was given for control of skeletal metastasis, relief of pain and, in the main was only limited.

The treatment employed was effective; however, not sufficiently so to account for the many years of survival after the onset of the disease. It seems likely that, through the entire clinical course, carcinomatous activity was taking place, primarily or secondarily, in various regions. The denuded surface of the primary field was finely granular and waxy in appearance and did not bleed easily with slight trauma. The inguinal lymph nodes felt like shot, were discrete and were slow in growth. From the standpoint of the therapeutic radiologist, the explanation of the longevity is found in the growth characteristic of this malignant lesion. Further investigation may furnish the answer to the problem. The many unusual features present in this case prompted the idea to include mention of carcinoma of Cowper's glands in this report The few cases of this condition that have been reported may be relevant to the present study because, in most of them, the tumors were suggestive of cylindroma, as was the tumor in this case, according to at least one pathologist who reviewed the tissue.

Case II (previously reported by Mayo and Barber). This patient was married and had had 2 children. She was forty-one years of age when she registered March 11, 1931. For at least two years the patient had known of a small lump in the left external genitalia.

Examination revealed a small, movable nodule in the left labium majus. The nodule was

widely excised and the pathologist's report read: "Adenocarcinoma (11 by 6 mm.) grade 1, of Bartholin's gland." The pathologist appended a note stating that he had not known this type of lesion of the labia to recur or metastasize.

Seven days later, prophylactic radium therapy was applied. The applicator was a small balsa wood block, previously described, and an American-type tube, the wall of which consisted of 0.5 mm. of silver and 1 mm. of brass, and which contained 92 mc. of radon. This apparatus was applied to the left labium majus for four hours.

In all reports, a good local result (primary field) was recorded. The last letter received was dated July 9, 1937.

Comment on Case II. The primary lesion was a growth of low grade of malignancy, probably encapsulated. It was widely excised and radium therapy was employed as a prophylactic procedure. The ultimate prognosis for this type of carcinoma is very good, however, when treatment is by surgery alone. The survival time from the onset of the disease to the last report was more than five years, probably seven or eight years. Further attempts at follow-up investigation have not been successful.

Case III (previously reported by Mayo and Barber). This patient was married but had had no children. She was fifty years of age when she registered June 26, 1933.

The patient reported having a lump in the vagina the size of a hen's egg. The onset, she said, was four years before and, during the interval, the lump had slowly enlarged. Six months before her registration, the patient had noticed a small lump in the right groin and recent swelling of the upper part of the right thigh.

Examination revealed a tumor in the situation of the right Bartholin gland and another tumor near the gland. Lymphedema affected the entire right leg and thigh and was graded 2 on a basis of grades 1 to 4, in which grade 1 indicates the least and grade 4 the greatest severity.

At operation, June 28, 1933, the small metastatic growth in the vicinity of the right Bartholin gland was excised with the gland. The pathologist's report read: "Nodule, vaginal wall, (3 by 2 cm.) squamous cell epithelioma grade 2." Postoperative radium therapy designed for palliation was begun July 5, 1933. The American-type tube, containing 48 mc. of radon, with additional lead filtration, was placed in two positions at the operative site and was kept in each position for eight hours.

The area of the right inguinal lymph nodes was mapped out in sixteen small fields. Sixteen small balsa wood blocks, were placed, four at a time, over these fields; the applications lasted for fourteen hours. Eight similar fields were treated in a similar manner in the area of the left inguinal lymph nodes.

The patient returned October 26, 1933. The condition at the operative site seemed satisfactory at that time but the lymphedema of the right leg persisted.

Roentgen therapy was given as follows: 200 kv., 50 cm. distance, 5 ma., 0.75 mm. copper and 1.0 mm. aluminum, time one hour and ten minutes to six large pelvic fields.

August 28, 1934, the patient reported by letter that the left leg had begun to swell five weeks previously.

The patient returned December 29, 1934, at which time lymphedema of both legs was present.

A letter was received from the attending physician February 27, 1935, reporting massive edema of both legs and of the left labium majus. However, the operative site was free of active malignant disease. The course of the disease was slowly and steadily retrogressive. Death was reported as having occurred September 1, 1936.

Comment on Case III. This patient had a vaginal tumor for four years before she sought treatment. Six months before institution of surgical treatment and limited radium therapy, metastasis to inguinal lymph nodes had taken place and, somewhat less time before institution of treatment, edema of the upper part of the right thigh had been noticed. Evidently, palliation was effected in that the primary lesion was controlled. The survival time from the onset of the disease was seven years.

Case IV. This patient was married and had had 4 children. She was seventy-one years of age when she registered December 11, 1933. The woman had found a small ulcer in the right

side of the vulva in April, 1932. The lesion had been curetted and treated by electric cauterization elsewhere. In July, 1933, the ulcer had recurred and, in November, 1933, the patient had found a tumor, the size of a hickory nut, in the right groin.

Examination at the Clinic revealed a region of infiltration, with ulceration, in the right labium majus and an enlarged right inguinal lymph node. The tumor of the right labium and region of Bartholin's gland and the enlarged lymph node of the right groin were removed surgically December 14, 1933. A rubber drainage tube was placed in the surgical wound of the right groin. Surgically, the lesion was considered to be a primary carcinoma of Bartholin's gland, metastasizing to the right inguinal lymph nodes. The pathologist's report read: "Squamous cell epithelioma grade 2 in both surgical specimens."

Radium therapy was applied twenty-four hours later. The American-type tube containing 50 mg. of radium sulfate (element) was introduced through the surgical drainage tube and was allowed to rest in two separate locations in the depth of the wound for fourteen hours in each location.

One vaginal applicator, cylindrically shaped, measuring about 5 cm. in length and 2.5 cm. in diameter, contained one American-type tube and additional filtration of 2 mm. of lead and 1 cm. of rubber was furnished; this device was placed in the vaginal cavity and was kept there for ten hours. Four American-type tubes in rubber tubing were strapped together to make a surface applicator. The apparatus was applied to the low angle of the surgical wound of the right vulva and was left in place for three and a half hours.

The patient revisited the Clinic, March 29, 1934. At this time her general condition was very poor on account of steady advance of the malignant disease and hemorrhage in the region of the metastatic growth in the right groin. The surgical site in the vagina and right side of the vulva seemed free of malignant activity.

The right inguinal region was mapped out in twenty-five fields and the small balsa block applicators were applied four at a time and were left in place for fourteen hours, until all fields had been covered. The same region was mapped out in three large fields and the large block applicator was applied to each field and was allowed to remain in place for twenty hours.

The patient returned May 2, 1934. Much palliation had occurred in that the malignant activity in the fields of treatment was reduced.

Two American-type tubes were placed in a shallow sinus in the right groin. The total radon content was 55 mc. and the duration of treatment was twelve hours. The inguinal region was mapped out in twelve small fields to which the small balsa wood blocks were applied four at a time and were left in place for fourteen hours each.

Death occurred July 16, 1934.

Comment on Case IV. The course in this case was modified by treatment given elsewhere. The primary lesion had metastasized to the inguinal lymph nodes at the time that radium therapy was applied. The treatment was designed for palliation only. The malignant process was locally arrested. Survival time from the onset of the disease was two years.

Case v. This patient was married but had had no children. She was forty-seven years of age when she registered December 29, 1934. For eight months she had noticed a painless swelling, the size of a walnut, in the left portion of the vulva, posteriorly. The tumor had been widely excised elsewhere September, 1934, but a pathologist's report was not available. The woman noted soreness in the perineum December 12, 1934, and a definite tumor, December 23, 1934.

Examination at the Clinic revealed a firm infiltration in the posterior lateral wall of the vagina at the introitus, beneath the skin of the perineum and near the anterior rectal wall. Inguinal adenopathy was not found.

The clinical diagnosis was carcinoma of Bartholin's gland, modified by surgery. A piece of tissue was removed from the wall of an ulcer which composed a portion of the partially necrotic, infiltrated tissue of the vaginal wall. The pathologist's report read: "Squamous cell epithelioma, grade 4."

On December 31, 1934, seventeen platinum-iridium points were placed in the tumor field and were left in place for forty-eight hours. Sacral block anesthesia was used. A few days later the vaginal applicator was placed, first in the middle, and then in the lower segment of the vagina and was left in these fields for fourteen and ten hours respectively. The American-type tube contained in a lead cylinder the wall of which was 2.0 mm. thick, all enclosed in a

finger cot, was placed in the depth of the crater-like ulcer in the vagina, where it was left for fourteen hours. The large block applicator was placed, first in the pubic and then in the vulval field for twenty hours each. Six small balsa wood block applicators were applied to treatment fields over the right and the left inguinal lymph nodes as a prophylactic procedure. Three blocks were applied at a time, on one side at a time, until all fields had been covered. Each field was exposed for fourteen hours.

The patient revisited the Clinic February 15, 1935. The ulcer in the vagina seemed healed. There was a small draining abscess (localized) in the left part of the perineum. Radium therapy was not applied at this visit.

The woman returned May 18, 1935. Her general health was very good. She was actively employed. A minimal, stellate scar replaced the ulcer of the vagina and vulva. There was a nodular infiltration about 1 cm. in diameter in the lower pole of the left labium majus. Nine platinum-iridium points were placed in this region of infiltration and were left in place for forty-eight hours. The large vaginal applicator was placed in the low vaginal segment and was left there for eight hours. Eight small balsa wood block applicators were applied in the regions of the right and of the left inguinal lymph nodes. Four of these were applied at a time, on one side at a time, until all fields had been covered. Following each application the applicators were left in place for fourteen hours.

The patient revisited the Clinic again October 23, 1935. She was in excellent general health. Minimal scars replaced infiltrated tissue. No active malignant infiltrations were made out. However, there was an indefinite, enlarged node in the right inguinal region. Eight small balsa wood blocks, previously described, were applied, four at a time, for fourteen hours each to the region of this enlarged node.

In a letter dated May 22, 1948, the patient was reported to be in excellent health and actively engaged in her own merchandise establishment.

Comment on Case V. Progress in this case was modified by surgical operation performed elsewhere, before the patient came to the Clinic. The lesion was of a high grade of malignancy. The radium therapy applied was designed for cure. The result obtained, as determined from the date of onset of the disease and the date of the last report, may be classed as, at the least, a fourteen year "cure."

Case VI. This patient was single and was fifty-three years of age when she registered June 27, 1935. She had found a lump between the vagina and rectum about June 1, 1935. She always had been of delicate health. Menopause had been brought on by roentgen therapy in 1929 because of menorrhagia. A nervous breakdown also was recorded in her history.

Examination revealed two tender nodules, one in the left paravaginal region and the other in the left pararectal region, infiltrating the inferior pole of the left labium majus. One mass was slightly fixed. One small, palpable, right inguinal lymph node was found. On proctoscopic examination, the following were found: a mass, measuring 3 by 6 cm., lying anterior to and to the left of the anus and lower part of the rectum, extending down to the external anal margin and adherent to the rectal and anal wall at the level of the anterior crypts. Bimanual pelvic examination and minimal laboratory determinations gave essentially negative results.

At operation, July 1, 1935, a nodule in the region of the left Bartholin gland or its duct was removed for biopsy. Several hard nodules extending into the rectovaginal septum were found. The pathologist's report read: "Tissue from region of left Bartholin's gland, squamous cell epithelioma grade 4."

Radium therapy as a palliative procedure was begun July 8, 1935. Two large, cylindrical vaginal applicators were placed one at a time, first in the deep and then in the middle vaginal segment. Treatment in each of these fields was for fourteen continuous hours. A rectal dilator containing three American-type tubes, containing a total of 133 mc. of radon equally distributed and filtered through an additional 1.0 mm. of brass and about 1.0 cm. of wood which composed the wall of the dilator, was placed in the anus and held firmly against the anal region for three hours. A large balsa wood block applicator was placed over the vulval area and was kept there for twenty hours. Roentgen therapy, 200 kv, 50 cm. distance, 10 ma., copper 0.75 mm. and aluminum 1.0 mm., time 28 minutes, was applied to each of four large pelvic fields; this was started on July 12, 1935 as daily treatments.

The patient revisited the Clinic October 28, 1935. Following the treatment she had tired easily, had been very weak and a distressing

diarrhea had lasted for several weeks. Her convalescence had been slow; however, her bowels were functioning regularly by the time of her return to the Clinic, her appetite was good and she had gained 4 pounds (1.8 kg.).

The mass in the lower pole of the left labium majus was considered to measure 3 by 4 cm. and to be movable. Further radium therapy was outlined. The large vaginal applicator was placed longitudinally, deep in the vaginal cavity and was left in place for fourteen hours. The rectal dilator was similarly placed and remained in position for two and a half hours. Seventeen platinum-iridium needles were placed in the infiltrated tissue of the perineal body, where they remained for forty-eight hours. Pus excaped through a puncture wound. It was enlarged and an iodoform wick was introduced. At this time the anal mucosa was ulcerated.

The patient revisited the Clinic February 25, 1936. Her general condition was slightly improved; however, she was uncomfortable on account of the perineal involvement. The size of the perineal tumor had remained about stationary; nevertheless, there was an increase in the extent of the infiltration into the rectovaginal wall. There was a small sinus, patent to gas, connecting the lower part of the rectum and the perineum in the tumor field.

Further radium therapy was outlined. The large vaginal applicator was applied, first in the deep and then in the middle vaginal segments; it remained in place for six hours in each location. Two American-type tubes containing a total of 113 mc. of radon, were placed in the sinus that has been described, where they were left for eight hours. Two similar tubes, containing 74 mc. of radon, were placed in the region of ulceration in the tumor field, where they remained for four and a half hours. Five gold radon seeds (wall 0.3 mm.), containing a total of 4 mc. of radon, were distributed in the infiltrated tissue of the rectovaginal septum.

Death was reported as of September 29, 1938, by letter, evidently caused by progression of the malignant disease.

Comment on Case VI. The rather superficial expression of the disease was favorably influenced by cautious radiation therapy, since palliation was all that could be expected. The malignant lesions were multiple when first seen and were considered inoperable. The time of survival was three years from the onset of the disease.

Case VII. This patient was married but had had no children. She was thirty-one years of age when she registered September 2, 1940. A left perineal tumor had been present for one year. About six times, a hemorrhagic, purulent material had been discharged from the mass and, each time, healing had followed. The tumor had been removed in the patient's home city in July, 1940. A slide of tissue from the tumor was sent to the Clinic where the pathologist who examined it reported: "Squamous cell epithelioma grade 2 (Bartholin gland)."

Examination revealed a large, recurring growth in the left side of the vagina. The inguinal lymph nodes were bilaterally enlarged. Minimal laboratory determinations gave essentially negative results.

At operation, September 5, 1940, the tumor was surgically removed. It had penetrated deeply near the pubic bone. The wound was left open for postoperative radium therapy. All tissue bearing lymph nodes in the inguinal and saphenous regions, and in the inguinal canal up to the level of the internal ring, was dissected out.

The pathologist's report read: "Vulva, squamous cell epithelioma grade 2. Lymph nodes, right side, metastatic squamous cell epithelioma grade 2. Left side, inflammatory tissue."

Twelve days after the operation that has been described, radium therapy was started. Two American-type tubes of monel metal, the walls of which were 1.5 mm. thick, containing 50 mg. of radium sulfate (element), were placed each in a lead jacket the wall of which was 2.0 mm. thick. The foregoing packets were placed singly in the distal and in the proximal portions of the vaginal wound. Each application was of ten hours' duration. The areas of the right and left inguinal lymph nodes were mapped out, each area in ten small fields, to which the small balsa wood block applicators were applied, about four at a time on the right and four at a time on the left, until all areas had been treated.

The patient returned January 7, 1941. The malignant process was active in the vagina and probably in the region of the inguinal lymph nodes.

A specimen then was removed from the anterior left wall of the vagina. The infiltrated tissue was cauterized. The pathologist's report read: "Squamous cell epithelioma grade 2."

Three days following the above procedure, contact radium therapy was outlined for the

vaginal fields. Three American-type tubes, packaged as previously described for a surface applicator, provided from 80 to 90 mc. hours of radiation per square centimeter for each application until all the surface of the area of involvement had been covered. In this case, six applications that varied from three to four hours each were required. The inguinal areas again were treated with the small balsa wood block applicators, as previously described.

The patient returned again May 9, 1941. Much palliation had been effected. Tissue change due to treatment was present in the vagina. No treatment was outlined at this visit.

On August 4, 1941, the woman returned again. The tissue change due to treatment had subsided. One application, for contact surface treatment, was made to an area of activity in the vagina (3 tubes for three hours). The inguinal lymph nodes seemed inactive.

When the patient returned on January 19, 1943, there was a crater in the left perineal area and in its deep portion was a urinary and fecal fistula. The anal area seemed intact. Edema of the left thigh and leg was graded 2. Bimanual rectal palpation revealed fixation and infiltration, graded 3 in extent, in the left adnexal tissues. The patient was actively employed. No treatment was recommended.

In the last letter received, dated January 3, 1944, the patient was reported to be bedfast.

Comment on Case VII. Progress in this case was modified by surgical operation performed before the patient came to the Clinic. We found an extensive vaginal carcinoma, with metastasis to the inguinal nodes. The vaginal growth was excised and the inguinal lymph nodes of both sides were dissected out. Postoperative radium therapy was limited in amount and the palliation secured was limited. Survival time from the onset of the disease was four years and four months to the time of the most recent report.

SUMMARY

The first patient of those whose cases have been reported was treated in 1924, and the last, in 1940. Some of the applicators used early in this experience are not employed today. The technique of radium therapy during the past twenty-four years has been definitely improved.

There were 7 patients in the group. All were married except 1 but, of those who were married, half had not had children. The youngest patient was thirty years of age and the oldest patient was sixty-nine years of age at the onset of the disease. The average age at registration was 47.1 years.

Two patients had had the condition for about four years, 2 patients for approximately two years, and 1 for one year before they came to the Clinic. The remaining 2 patients reckoned their illness in terms of months up to the time when we first saw them.

On admission, conditions were as follows: In Case II the primary lesion was clinically localized. The primary lesion in Case I had invaded the anal sphincter muscle and the inguinal nodes were enlarged. In Case III multiple tumors were present in the region of Bartholin's gland and inguinal lymph nodes were clinically involved. The primary lesion was ulcerated in Case IV and metastasis to the inguinal lymph nodes had taken place. The patient in Case V presented a large, recurring, ulcerated tumor but no definite inguinal adenopathy. In Case VI were multiple lesions in the primary field, adherent to the anal and rectal wall with involvement of inguinal nodes. A large, recurring tumor, with metastasis to the inguinal lymph nodes, was present in Case VII.

All primary lesions were studied microscopically. Five lesions are reported to be squamous-cell epitheliomas and 2, adenocarcinomas. The adenocarcinomas were of low grade of malignancy; 1 was of grade 1 and the other of grade 2. The squamous-cell epitheliomas also favored the low grades; 3 were of grade 2 and 2 were of grade 4. When all lesions are considered, 5 were of low grade and 2 of high grade of malignancy.

In 5 cases the primary lesion was surgically excised at the Clinic. In 1 of these 5 the excision was partial. Of the 2 remaining cases, in 1 wide excision had been performed before we saw the patient and no excision was performed at the Clinic. In the remain-

ing case of the 2, tissue was removed only for biopsy.

All patients received radium therapy. In 1 case radium was used prophylactically. A complete course of radium therapy designed for cure was given in 1 case. In 1 case radium therapy which originally was intended for cure was later limited to use for palliation. Four patients received limited radium therapy, designed for palliation throughout. Three of the 7 patients received supplemental roentgen therapy.

The primary lesion in only 2 cases was considered localized while in the remaining cases there was local dissemination or metastasis to the inguinal lymph nodes.

Four patients are known to have died of the disease, 1 patient was bedfast in 1944, 1 was living and seemed well in 1948, and 1 could not be followed after 1937. The longest survival from the onset of the disease was in Case 1, in which the lesion was considered an adenocarcinoma, grade 2; the patient survived twenty-six years after onset of the disease. The second longest survival time after onset of the disease was in Case v, in which the diagnosis was squamous-cell epithelioma, grade 4. The woman was in good health fourteen years after the onset of the disease. Next in order of duration of life after onset of the disease was the patient of Case II, whose lesion was diagnosed adenocarcinoma grade 1. At the time when this report was written she was lost to our follow-up system; however, she was known to be in good health seven or eight years after onset of the disease. In Case III, in which the diagnosis was squamous-cell epithelioma grade 2, the survival time was seven years after onset of the disease. In Cases VII and VI, in the former of which the diagnosis was squamous-cell epithelioma grade 2 and, in the latter, squamous-cell epithelioma grade 4 the patients were known to have lived, respectively, more than four years and three years after the onset of the disease. The shortest survival time after onset of the disease was two years, occurring in Case IV, in which the diagnosis was squamous-cell epithelioma grade 2.

CONCLUSIONS

1. Carcinoma of Bartholin's glands (greater vestibular glands) is rare and the carcinomas tend to be of low grade of malignancy.

2. Carcinoma confined to a Bartholin gland, of low grade of malignancy, if wide excision is followed by prophylactic radium therapy, should not recur.

3. Clinically extensive carcinoma of a Bartholin gland, localized to the primary field, if treated with radium designed for cure, regardless of grade, may not recur.

4. Surgery, radium therapy and roentgen therapy in combination constitute effective methods for control of carcinoma of Bartholin's glands.

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EFFECTS OF REPEATED LOW DOSES OF NEUTRONS ON THE ESTROUS CYCLE OF THE WHITE RAT*

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IN THE course of investigating the general effects of repeated low doses of neutrons on white rats, it was noted that doses of 1.8 n given six days a week for seven to nine months caused a reduction in the growth rate but no change in the picture of the peripheral blood.[5] Among the small number of animals, a large percentage of those given the low doses and 2 animals given twelve daily doses of 10 n each developed tumors of the breast, kidney and lymphoid tissue.

In continuing these investigations, the first phase undertaken was a study of the estrous cycle of the white rat by the vaginal smear method of Long and Evans[6] to determine whether the cycle was affected by neutron irradiation. Bischoff *et al.*[1] irradiated six week old mice with single doses of 200 and 400 r of roentgen rays. At the 200 r level, irradiation markedly reduced the frequency of estrus, increased its frequency during the fourth month, followed by a six month period during which estrus did not differ significantly from that of the controls. With a dose of 400 r, estrus in the mice was abolished following irradiation and the frequency of estrus established for the controls was not attained throughout a thirteen month period. Drips and Ford[2] found, on irradiating a group of rats with 1/10 to 1/15 the human erythema dose of roentgen rays, some temporary irregularities in the estrous cycle. Skipping of one or two cycles and prolongation of the cornified stage were the principal variations observed. Slight congestion of the ovaries in those animals killed within a few days after irradiation was the only pathological change.

The above data indicate that some effects of neutrons on the estrous cycle of the rat are to be expected. Furthermore, in light of the recent publication of Gates and Warren[4] on the vaginal smear as a diagnostic aid in the early detection of uterine cancer in humans, it was thought that the appearance of tumors induced by neutron irradiation might be reflected in the estrous cycle of the rat.

EXPERIMENTAL PROCEDURE AND RESULTS

Forty-six female white rats, varying in age from forty-two to sixty-six days, were taken from fourteen litters raised in the colony of the Biochemical Research Foundation, and were divided into two groups of 23 each. One group constituted the experimental animals to be irradiated and the other served as the non-irradiated control. All time data are given in terms of the number of days after the date the two groups were established.

Beginning with the twenty-fifth day of observation, when the rats were from sixty-seven to ninety-one days old, daily vaginal smears were made on all animals according to the method of Long and Evans[6] to establish the normal picture of the cycle. Smears were then made almost daily until the 176th day of observation when the rats were 218 to 242 days old. Irradiation of the experimental group began on the fifty-second day and continued until the ninety-fourth day at which time irradiation was discontinued. Vaginal smears showed that the non-irradiated group exhibited normal and regular cycles of from four to six days' duration. In contrast, the irradiated group showed disruption of the pattern of the cycle during and following the period of irradiation (Fig. 1) with finally the reappearance of a normal cycle. No abnormal cells were observed in any of the vaginal smears.

The animals were irradiated by the cyclotron of the Biochemical Research Foundation under the direction of Dr. Theodore Enns according to the procedure described previously by Enns *et al.*[3] A daily dose of 3 n was given in approxi-

* From the Biochemical Research Foundation, Newark, Delaware.

mately seven minutes, six days a week, until the total dose of 111 n (37 doses in a total of 42 days) had been administered. This was the only feature in which the treatment of the irradiated groups differed from that of the controls.

At intervals during the investigation, the animals were weighed and these results, in terms of the average for each of the two groups, are given in Figure 2. Hematological studies indicated that the only observable changes brought about by the neutron irradiation was a lowering of the white blood cell count to a minimum of 6,000 to 7,000 per cu. mm. after sixteen doses of neutrons, followed by recovery.

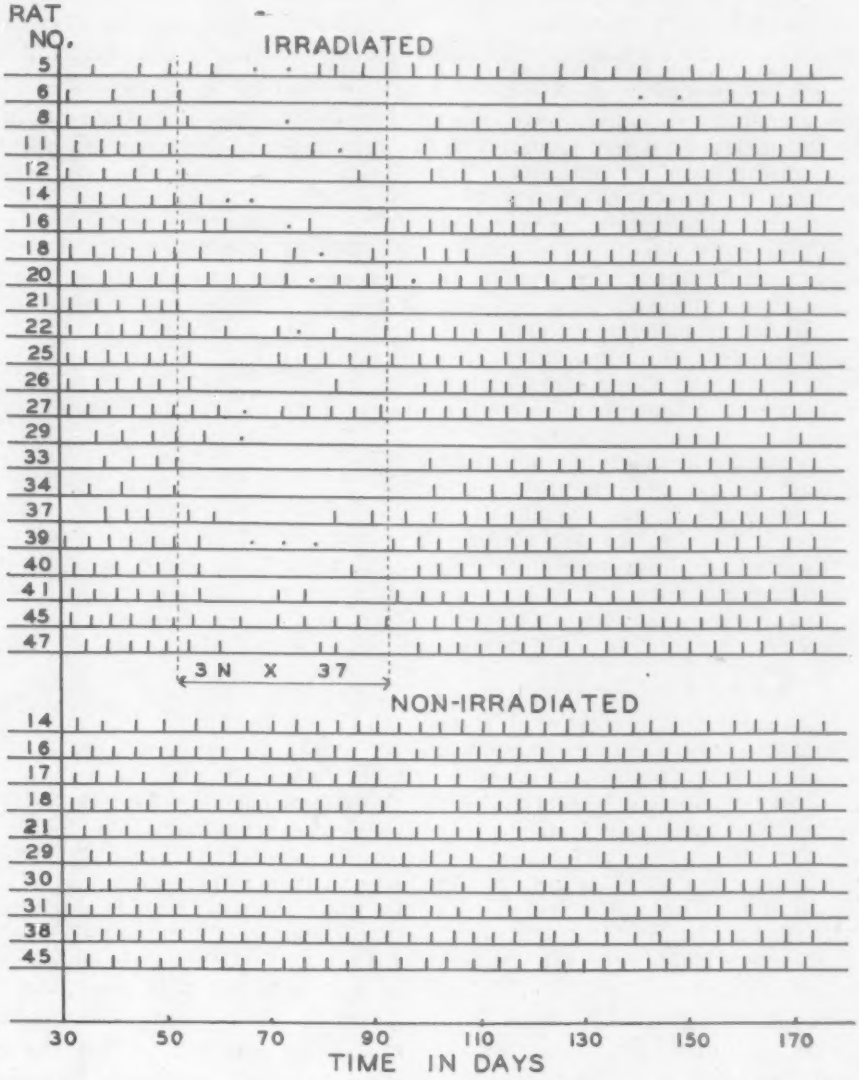

FIG. 1. Frequency of the estrous cycle in the irradiated and in some of the non-irradiated rats. The vertical line indicates the time of appearance of the so-called "cheesy-cornified" stage (stage 3 of Long and Evans). A dot indicates an abnormal cycle.

DISCUSSION

The estrous cycles of all irradiated rats and of a representative number of the non-irradiated are represented diagrammatically in Figure 1. In these figures, the vertical line indicates the conspicuous so-called

"cheesy-cornified" stage of a normal cycle, which is stage 3 of Long and Evans.[6] In some instances, especially during the period of irradiation, the "cheesy-cornified" stage was not apparent although there occurred occasionally a stage showing some cornified cells but always mixed with some epithelial cells, a condition designated in Figure 1 by a dot.

The radiation level of 3 n per day was very satisfactory for demonstrating the effect of neutrons on the estrous cycle. From Figure 1 it can be seen that a wide range of effects on the cycle was produced. In rats 6, 8, 21, 29, 33, and 34, the normal cycle was completely inhibited during the period of irradiation and for a varying length of time afterwards. The maximum effect was shown by rats 21 and 29 which did not show a return to a normal cycle for forty-six to fifty-five days, respectively, after termination of irradiation. In contrast to the above reaction, only a slight irregularity in the estrous cycle was observed for rats 5, 20, 22, 27, and 45. The other rats of the irradiated group showed changes in the cycle varying widely between these extremes.

None of these rats showed a prolonged or continuous or increased frequency of estrus during the period of observation, as was found in mice following roentgen-ray doses of 200 and 400 r by Bischoff *et al.*[1]

None of the irradiated rats could be considered ill during the period of observation although they all showed a low white blood cell count together with an initial loss of weight. As is shown in Figure 2, following a slight loss in weight, growth was resumed but at a rate somewhat below that of the corresponding controls. In this connection it is interesting that thirty-seven doses of 3 n each had a more profound effect on the rats than the 172 or 251 doses of 1.8 n each, reported previously by Leitch.[5] In the latter experiments, a reduced growth rate was the only effect of the irradiation, there being no initial weight loss and no hematological effects. From these two series of experiments it would appear that the daily doses of 1.8 and 3 n lie in a very critical range that requires further investigation.

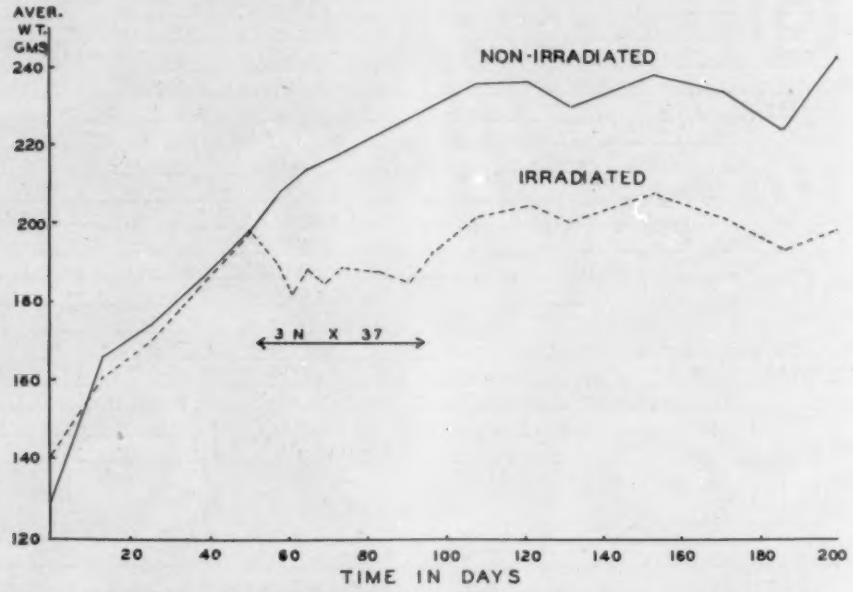

Fig. 2. Average weights of the irradiated and the non-irradiated rats during the period of investigation.

Neutron irradiation affects the estrous cycle of the white rat even when low doses are used. However, considerable more data

dealing with the effects of varying neutron doses given during different time intervals are required before the full relationship between neutron dose and effects on the estrous cycle can be worked out. Furthermore no conclusions can be drawn at this time concerning the mechanism of this action.

Since the animals used in this experiment are still being observed for the induction of tumors, no data can be reported at the present time on either gross or microscopical pathology. It can be reported now that rats 5, 18, 26, and 27 have already developed tumor-like swellings in the mammary region. Reference to Figure 1 indicates that these 4 rats showed no unusual changes in the estrous cycle as a result of irradiation.

SUMMARY

Neutron bombardment of twenty-three rats at the rate of 3 n daily for thirty-seven exposures caused a disruption of the estrous cycle as indicated by vaginal smears, a retardation of growth and temporary reduction in white blood cells in the circulating blood.

Swellings appeared in the mammary region of four rats uncorrelated with estrous cycle variations.

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PHARMACOLOGICAL REACTIONS OF SERA AND DRUGS IRRADIATED WITH ROENTGEN RAYS OF VARYING WAVELENGTH*

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PHYTOTOXICITY

TWENTY-FIVE years ago, one of the authors, being interested in some of the general laws of pharmacology, began a study of the relative sensitivity of animal and vegetable protoplasm to various drugs and chemicals.[1] This marked the beginning of a new department of biology to which the name of *phytopharmacology* was given. It was soon discovered that living plant-physiological test objects were much more sensitive to certain poisons than animal tissues are and, vice versa, other poisons were much more toxic for living animal protoplasm than for vegetable protoplasm. As a result of these experiments, it could be generally stated that poisons or toxins derived from animals are much more poisonous for vegetable protoplasm than for animal protoplasm and, vice versa, most of the poisons derived from the plant world are usually much more poisonous for living animals than for living plants. This general observation was particularly true of toxins present in the blood of human beings. By means of phytopharmacological tests it was definitely demonstrated that there were poisonous substances or toxins present in certain pathological conditions which could not be demonstrated by zoological experiments nor by ordinary chemical methods.

The effects of drugs and poisons on plants can be studied in many ways. These methods have been described elsewhere.[2] For convenience and for quantitative determination, it was found that the growth or elongation of the straight single roots of *Lupinus albus* seedlings grown in plant physiological solutions under standardized ecological conditions were most suitable for practical medical purposes. As published elsewhere,[3] it was shown that normal blood sera dissolved in 1 per cent solutions of Shive[4] medium caused but little inhibition in the root growth of lupine seedlings. The phytotoxic index or ratio of growth in a 1 per cent serum solution compared with controls grown in plant physiological saline solution ranges from 70 to 75 per cent, and this is true for blood sera of all animals, both warm-blooded and cold-blooded, with the exception of reptiles.[5] In the case of human blood serum, a number of pathological conditions were found to yield much more toxic effects and have lower indices of growth. This was true of the following conditions: catamenia or menstruation, pernicious anemia, trachoma, leprosy, and especially the very grave skin disease known as pemphigus. Each of these diseases yields a characteristic phytotoxic effect, and these blood sera can be differentiated from each other by various other properties, particularly by their responses to ultraviolet radiations.

RADIATION AND PHARMACOLOGICAL STUDIES

Even twenty years ago when the phytotoxic properties of pernicious anemia were first discovered by Macht, it was found that exposure of such blood sera in quartz containers to an ultraviolet mercury vapor lamp for a few minutes was followed by a complete detoxification of the serum as indicated by phytopharmacological assay.[6] Macht and Anderson went further and

* Presented at the Winter Meeting of the Optical Society of America, New York, N. Y., March 5, 1948.
† Dr. Ostro died on May 12, 1948.

found that therapeutic irradiation of patients suffering from pernicious anemia produced a diminution in toxicity or even complete detoxification of their blood, concurrently with improvement in their blood morphology and clinical improvement of the patients' general health. Curiously enough, however, when similar irradiation experiments were tried in quartz containers on blood sera from leprosy and trachoma and on menstrual serum, no detoxification occurred. Neither was there any detoxification produced by such ultraviolet irradiation in the blood of pemphigus.[7]

In the last three years, the authors have been engaged in a study at the Sinai Hospital of Baltimore, of the effects of roentgen rays on various properties of the blood and on the pharmacological properties of a number of drugs. For this purpose, a Westinghouse roentgen therapy machine was employed with and without filters. It was found in the experiments on blood that when normal serum is exposed to roentgen rays filtered through a composite filter of 1 mm. Al and 2 mm. Cu, or through a filter of 1 mm. Al and 0.5 mm. Cu, its phytotoxic properties were either unchanged or usually made more toxic. On the other hand, when the blood serum of patients afflicted with pemphigus was treated with roentgen rays filtered through a composite filter, its characteristic toxic properties were destroyed. This occurred in so many experiments that the irradiation method is now employed in this laboratory as a confirmatory test for the diagnosis of pemphigus.[8] Briefly stated, an ordinary phytopharmacological examination of pemphigus serum gives a *toxic* index of growth but when the same serum is treated with filtered roentgen rays the *toxicity disappears*. The two tests together establish a positive diagnosis of pemphigus because no other skin disease gives the same reactions. The factors employed in the irradiation are 200 kv., 20 ma., and target distance of 50 cm.

The present authors, furthermore, found that the toxicity of the blood in true pernicious anemia is also rapidly destroyed by the above roentgen rays, filtered through a composite filter. On the other hand, catamenial blood serum, the serum of trachoma and leprosy blood were not detoxified by such rays when tested by phytopharmacological methods.

Two other blood conditions yielded interesting results in connection with irradiation studies. The authors found that the blood serum of hemophiliacs can be made to clot more quickly by short (but not prolonged) exposures to specially filtered roentgen rays.[9,10] Again, more recently, studies have been made by one of the authors on the phytopharmacological properties of bloods from all kinds of mental diseases, and it was found that all true psychoses yield blood sera which are toxic for plants and the toxicity can be measured quantitatively by phytopharmacological methods. These blood sera from cases of psychoses are very quickly detoxified when treated with small doses (60 to 100 roentgens) of roentgen rays filtered through a composite filter.

The laboratory observation in vitro in regard to the detoxification of pemphigus serum by roentgen irradiation warranted a trial of roentgen therapy in 2 patients dying with pemphigus vulgaris. The idea was to endeavor to produce detoxification of the pemphigus poison by small doses of deeply penetrating roentgen rays. These patients were given short radiation over the hepatic and splenic regions. The results were amazing. The patients' blood was detoxified, as indicated by pharmacological tests described above, and the clinical condition of the patients was improved. Both of these patients are alive and in good health at the writing of this paper, three years after the beginning of the disease,* and this is itself a remarkable record for the usually fatal disease, pemphigus vulgaris.[11] Since the initiation of these radiotherapeutic studies, a series of other patients was given similar treatment, and more or less improvement was noted in 75 per cent of them. These

*Also in March, 1949.

are described elsewhere. [12] Here again the factors used were 200 kv., with 20 ma. and target distance of 50 cm.

EFFECTS OF DIFFERENT FILTERS

Perhaps the most interesting observations made by the authors from the standpoint of biophysics was the undoubted fact, as far as biological reactions are concerned, that the detoxification of pemphigus serum both in vitro and in vivo was produced best only when short roentgen rays were employed, obtained by filtration through a composite filter of 1 mm. Al and 2 mm. Cu. Thus, for instance, when pemphigus blood serum was treated in vitro with these rays in doses of 100 r, complete detoxification occurred. On the other hand, however, when another sample of the same original serum was treated with exactly the same dosage, 100 r, using 0.5 mm. Cu filter, very little or no detoxification occurred. Apparently there was a qualitative difference in the biological effect of the rays taking place, which is contrary to the usual teachings of physicists.

In order to clarify as much as possible this puzzling observation, the aid of a well known physicist was enlisted for further research on the problem. Dr. Scott W. Smith, x-ray physicist at the National Bureau of Standards, Washington, D.C., was invited to calibrate the roentgen apparatus employed for therapy at the Sinai Hospital, Baltimore, and to aid in constructing a physical apparatus by which roentgen rays differing widely in their quality range could be employed for pharmacological research. This was done by Dr. Smith as follows: Five different sets of filters were selected, their absorption curves and half-layer values were determined and different voltages were selected which would yield exactly the same intensity or dosage of roentgen rays and yet furnish aggregates of roentgen rays definitely different in quality. Table 1 gives the physical data which we obtained in our biophysics experiments. For briefness, the five filters are designated as A, B, C, D, E. Starting with this apparatus, we exposed specimens of various kinds of pathological blood sera as well as a number of drugs, and after exposing them to exactly the same dosages of the roentgen rays, experiments were made to ascertain if any differences in the pharmacological

Table I

PHYSICAL FACTORS FOR THERAPY CONE 15 BY 15 CM.

Symbol	Kv. (peak)	Ma.	Filter	r/min.	Time for 100 r
A	200	20	0.93 mm. Cu	24.0	4 min. 10 sec.
B	160	20	0.62 mm. Cu	13.5	7 min. 24 sec.
C	126	20	0.31 mm. Cu	8.2	12 min. 12 sec.
D	100	20	6.25 mm. Al	3.4	29 min. 24 sec.
E	80	20	4.16 mm. Al	1.35	74 min. 0 sec.

Table II

PHYSICAL FACTORS FOR THERAPY CONE 6 BY 8 CM.

Symbol	Kv. (peak)	Ma.	Filter	Half-Value Layer	r/min.	Time for 100 r	Effective Wavelength
A	200	20	0.93 mm. Cu	1.03 mm. Cu	20.70	4 min. 50 sec.	0.17 Å
B	160	20	0.62 mm. Cu	0.67 mm. Cu	11.70	8 min. 34 sec.	0.19 Å
C	126	20	0.31 mm. Cu	0.28 mm. Cu	7.10	7 min. 6 sec.	0.27 Å
D	100	20	6.25 mm. Al	4.10 mm. Al	2.94	34 min. 0 sec.	0.39 Å
E	80	20	4.16 mm. Al	3.00 mm. Al	1.17	85 min. 30 sec.	0.52 Å

properties could be detected. As will be seen, the results established conclusively that there were marked differences in the pharmacological effects produced by the rays filtered through different filters.

Table I shows the physical data established for the roentgen apparatus employing a therapy cone of 15 by 15 cm. Table II gives the factors which we employ more frequently with a therapy cone 6 by 8 cm. for irradiating sera and drugs in small open top glass containers at a distance of 50 cm.

IRRADIATION OF BLOOD SERA

The changes produced in sera and drugs by irradiating them with roentgen rays, employing various filters, administered in exactly the same dosages were studied in some cases by zoopharmacological methods, in other cases by phytopharmacological methods, and in still other cases by biochemical tests. The results obtained are here briefly presented. The blood sera studied came from the following pathological conditions: catamenia, trachoma, leprosy, pemphigus, pernicious anemia, and psychoses. It was found that menstrual serum and the sera of leprosy and trachoma irradiated with roentgen rays passing through various filters did *not change* the phytotoxicity of these bloods as studied on seedlings of *Lupinus albus*. This is shown in Tables III and IV. On the other hand, the blood sera from all kinds of psychoses and from pemphigus were markedly affected by irradiating them with *some qualities* of roentgen rays and not affected by other qualities. This is strikingly illustrated by Tables V and VI, both of which are composite tables summarizing the results obtained in a large number of experiments. Thus, for instance, it will be seen that pemphigus serum is markedly detoxified when a composite filter of 1 mm. Al and 2 mm. Cu is used, whereas the same serum treated with roentgen rays passed through a filter of 0.5 mm. Cu was only slightly detoxified. Of the five individual filters, A, B, C, D, E, the most striking effect was obtained with Filter A which produced

Table III

RESISTANT BLOOD SERA

Leprosy Serum				Catamenia Serum			
Method of Roentgen Treatment	Duration	Dosage	Phytotoxic Index	Method of Roentgen Treatment	Duration	Dosage	Phytotoxic Index
Untreated control 1% solution	—	—	52%	Untreated control 1% solution	—	—	48%
Using Filter A	5 min.	100 r	49%	Using Filter A	5 min.	100 r	46%
Using Filter B	9 min.	100 r	52%	Using Filter B	9 min.	100 r	44%
Using Filter C	14 min.	100 r	56%	Using Filter C	14 min.	100 r	48%
Using Filter D	34 min.	100 r	50%	Using Filter D	34 min.	100 r	49%

Table IV

TRACHOMA BLOOD SERUM

Irradiated through Composite Filters of 1.0 mm. Al plus 2.0 mm. Cu

Specimen No. 1	Phytotoxic Index	Specimen No. 4	Phytotoxic Index
Before irradiation	65%	Before irradiation	57%
After 110 r	57%	After 110 r	57%
Specimen No. 2		Specimen No. 5	
Before irradiation	55%	Before irradiation	55%
After 110 r	53%	After 110 r	47%
Specimen No. 3		Specimen No. 6	
Before irradiation	58%	Before irradiation	59%
After 110 r	61%	After 110 r	57%

TABLE V

PSYCHOTIC BLOOD SERA
(POOLED SPECIMENS)

Schizophrenic Sera				Manic Depressive Sera			
Method of Roentgen Treatment	Duration	Dosage	Phytotoxic Index	Method of Roentgen Treatment	Duration	Dosage	Phytotoxic Index
Untreated specimen	—	—	57%	Untreated specimen	—	—	50%
Using Filter A	5 min.	100 r	79%	Using Filter A	5 min.	100 r	71%
Using Filter B	9 min.	100 r	68%	Using Filter B	9 min.	100 r	62%
Using Filter C	14 min.	100 r	61%	Using Filter C	14 min.	100 r	54%
Using Filter D	34 min.	100 r	57%	Using Filter D	34 min.	100 r	50%
Using Filter E	85 min.	100 r	54%				

TABLE VI

PEMPHIGUS SERUM (POOLED SPECIMENS)

Method of Roentgen Treatment	Duration	Dosage	Phytotoxic Index of Growth
Untreated specimen	—	—	42%
Using Filter 0.5 mm. Cu	4 min.	100 r	52%
Using Filter 2.0 mm. Cu	6 min.	100 r	76%
Using Filter A	5 min.	100 r	73%
Using Filter B	9 min.	100 r	57%
Using Filter C	14 min.	100 r	46%
Using Filter D	34 min.	100 r	40%
Using Filter E	85 min.	100 r	35%

marked detoxification. Filter B produced slight detoxification while Filters C and D produced no effect and Filter E actually rendered the serum more phytotoxic. Very similar results were obtained with irradiating blood from psychotic patients. Blood sera from patients with pernicious anemia were also found to be detoxified by roentgen rays passed through a composite filter (Table VII).

Another interesting series of experiments was carried out with the blood of a patient suffering from hemophilia. This particular patient hospitalized in the wards of Sinai Hospital usually exhibited a very marked prolongation of his clotting time. Specimens of his blood were taken from an arm vein and the influence of roentgen rays of various wavelengths on clotting time was studied, as shown in Table VIII. Here it will be noted that the unirradiated serum took four hours forty minutes to clot whereas the normal clotting time in humans studied by the Lee-White method varies from five to ten and not more than fifteen minutes. When the whole blood from this hemophilia patient treated with roentgen rays passed through Filter A the clot-

TABLE VII

PERNICIOUS ANEMIA SERUM
(POOLED SPECIMENS)

Method of Roentgen Treatment	Duration	Dosage	Phytotoxic Index
Untreated control 1% solution	—	—	42%
Using filter of 1.0 mm. Al plus 2.0 mm. Cu	2 min.	36 r	56%
Using filter of 1.0 mm. Al plus 2.0 mm. Cu	4 min.	72 r	59%
Using filter of 1.0 mm. Al plus 2.0 mm. Cu	6 min.	108 r	67%
Using filter of 1.0 mm. Al plus 2.0 mm. Cu	8 min.	144 r	72%

ting time was cut down to one hour three minutes. Irradiation through Filter B prolonged the clotting time to one hour thirty-one minutes, whereas irradiation through Filter D prolonged it to two hours three minutes (Table VIII). In this case there was definitely a marked difference produced by equivalent dosages of roentgen rays but of different qualities. However, as has already been stated by the authors in an arti-

TABLE VIII

HEMOPHILIA PATIENT
Nov. 12, 1947

Specimen	Clotting Time of Whole Blood
Untreated Serum	4 hr. 40 min.
Irradiated with 100 r Filter A	1 hr. 3 min.
Irradiated with 100 r Filter B	1 hr. 31 min.
Irradiated with 100 r Filter D	2 hr. 3 min.

cle on hemophilia, increasing the dosage beyond certain limits may *reverse* the thromboplastic effect of the roentgen rays.

IRRADIATION OF DRUGS

In addition to studies on blood we examined the effects of roentgen irradiation in vitro, using various filters, on the following drugs: tincture of digitalis, digitoxin, the venom of *Crotalus atrox* (rattlesnake), the neurotoxin of *Naja tripudians* (cobra venom), solutions of penicillin, both crystalline and amorphous, and streptomycin. The action of various qualities of roentgen rays on tincture of digitalis was studied in a large number of experiments by phytopharmacological methods,[13] on the one hand, and by intraperitoneal injections in white mice.[14] Tables IX and X reveal again the difference in the effects produced when different filters are used. This is especially well illustrated by the phytopharmacological assay which is a composite table of thirteen experiments using all five filters. It will be seen that irradiation through Filters A and B produces a marked decrease in the toxicity of digitalis for *Lupinus* seedlings.

TABLE IX

PHYTOPHARMACOLOGICAL ASSAY OF DIGITALIS TINCTURE. COMPOSITE TABLE OF 13 EXPERIMENTS WITH 1 PER CENT SOLUTION

Method of Roentgen Treatment	Duration	Dosage	Phyto toxic Index of Growth
Untreated specimen	—	—	51%
Using Filter A	5 min.	100 r	73%
Using Filter B	9 min.	100 r	72%
Using Filter C	14 min.	100 r	62%
Using Filter D	34 min.	100 r	58%
Using Filter E	85 min.	100 r	57%

Irradiation through Filter C produces only a slight effect while irradiation through Filters D and E produces still less effect. The protocols shown in Table X illustrate the results obtained with digitalis injections in mice. Here again it will be noted that irradiation through Filter A reduces the potency of digitalis much more than irradiation through Filter C, as indicated by the mortality of animals obtained in the experiments.

The effects of roentgen rays of various qualities on the most active principle of digitalis, namely digitoxin,* was studied by a chemical method, as well as on plants. The effects of irradiation of digitoxin in

TABLE X

DIGITALIS EXPERIMENTS ON MICE
OCT. 29–NOV. 7, 1947
Dosage 4 mg. per gram weight

I. Normal Tr. digitalis	4 mg. per gm. wt. Mortality 100% Phytotoxic index 51%
II. Irradiated through Filter A, 300 r	4.5 mg. per gm. wt. Mortality 25% Phytotoxic index 72%
III. Irradiated through Filter C, 300 r	4.5 mg. per gm. wt. Mortality 35% Phytotoxic index 62%

* The digitoxin was obtained from the Winthrop Company through the courtesy of their research director, Dr. Maurice Tainter.

TABLE XI

INFLUENCE OF ROENTGEN IRRADIATION ON DIGITOXIN (WINTHROP)
METHOD OF ANDERSON AND CHEN
Colorimetric Readings with Klett-Summerson Photoelectric Colorimeter

Concentration of Solution	Roentgen Treatment	Dosage	Phytotoxic Index	Colorimeter Reading
1:20,000 in alcohol	Not irradiated	—	74%	70.0
1:20,000 in alcohol	Using Filter A	200 r	50%	66.5
1:20,000 in alcohol	Using Filter B	200 r	48%	62.0
1:20,000 in alcohol	Using Filter C	200 r	46%	56.0
1:20,000 in alcohol	Using Filter D	200 r	44%	52.0

TABLE XII

COBRA VENOM (*Naja tripudians*)
COMPOSITE TABLE
SOLUTION IN PHYSIOLOGICAL SALINE 1:100,000

Method of Roentgen Treatment	Duration	Dosage	Phytotoxic Index of Growth
Untreated specimen	—	—	75%
Using Filter A	5 min.	100 r	82%
Using Filter B	9 min.	100 r	86%
Using Filter C	14 min.	100 r	90%
Using Filter D	34 min.	100 r	93%

alcoholic solutions were compared colorimetrically by the method of Anderson and Chen.[15] Table XI shows a definite difference produced by irradiation through the different filters (Table XI).

The effects of cobra venom were studied on both plants and animals. Assays of the solutions of cobra venom irradiated by different qualities of roentgen rays were made by the method of Macht on white mice.[16,17] It will be noted from Table XII that roentgen irradiation of cobra venom produces a deterioration or attenuation of the venom, but here again there was a difference in the degree of deterioration of the venom irradiated using Filters A and B, on the one hand, and of the venom irradiated using Filters C and D, on the other. Similar differences in toxicity of cobra venom were noted in phytopharmacological experiments on *Lupinus albus* seedlings[18] and here also a parallel difference in degree of decomposition was found in regard to roentgen rays filtered by different filters (Table XIII). The

TABLE XIII

ASSAY OF COBRA NEUROTOXIN ON BASIS OF 1 MOUSE UNIT PER 20 GM. MOUSE

I. Unirradiated solution	Mortality 90%
II. Irradiated 100 r through Filter A	Mortality 50%
III. Irradiated 100 r through Filter C	Mortality 30%

TABLE XIV

VENOM OF *Crotalus atrox* SOLUTION 1:5000
COMPOSITE TABLE

Method of Roentgen Treatment	Duration	Dosage	Phytotoxic Index of Growth
Untreated specimen	—	—	52%
Using Filter A	5 min.	100 r	64%
Using Filter B	9 min.	100 r	67%
Using Filter C	14 min.	100 r	79%
Using Filter D	34 min.	100 r	82%

venom of the rattlesnake was studied on the growth of plants as well as in regard to its toxicity for mice (Table XIV). The results obtained also definitely indicated a difference in pharmacological reaction produced in samples of the same venom solution treated with roentgen rays of different qualities.

In regard to the very important class of antibiotics, penicillin and streptomycin,

the pharmacological reactions were studied by phytopharmacological methods, on the one hand, and by biochemical methods, on the other. These studies are still in progress but it can be definitely stated here that a marked difference in pharmacological properties of both drugs was found between samples treated with roentgen rays passed through a composite filter of 2 mm. Cu and those treated with roentgen rays passed through a filter of 0.5 mm. Cu. Full data will be published in a separate paper.

Among the biochemical tests employed in studying penicillin as well as some of the blood sera were experiments concerned with oxidation-reduction phenomena. The Thunberg method was employed.[19,20] These studies are still in progress but it may be stated here that there was a definite difference noted after treatment of specimens of the sera and antibiotics, with roentgen rays passed through different filters. A very striking illustration is shown in Table xv which gives the results obtained with a specimen of pooled pemphigus serum both in regard to its phytotoxic index of of growth for *Lupinus albus* roots and the time required for decolorization of methylene blue by Thunberg's method.

Table XV

OXIDATION-REDUCTION EXPERIMENT (THUNBERG'S METHOD)
EMULSION OF WATER-SOAKED *Lupinus albus* SEEDS

Serum Examined	Roentgen Treatment	Phytotoxic Index	Time Required for Decolorization of Methylene Blue
Normal human serum	Untreated	75%	50 min.
Pooled pemphigus serum	Untreated	42%	2 hr. 0 min.
Pooled pemphigus serum	100 r through filter of 1 mm. Al plus 2 mm. Cu	80%	68 min.
Pooled pemphigus serum	100 r through filter of 1 mm. Al plus 0.5 mm. Cu	54%	1 hr. 45 min.

COMMENTS

While the above investigation is still in progress certain tentative conclusions are warranted on the basis of the numerous radiation and pharmacological experiments performed by the authors.

In the first place, roentgen rays produce marked changes in the pharmacological properties of some kinds of sera, and few or none on sera from other pathological conditions.

In the second place, similar changes in the potency of certain drugs are produced by irradiation with roentgen rays, some drugs developing a greater toxicity, and others revealing a diminished physiologic potency.

In the third place, in view of the quantitative pharmacological assays and the carefully controlled irradiation experiments with different filters and equivalent doses of roentgen rays, there is no doubt that roentgen rays of different wavelength produce changes in blood sera and in a number of drugs or poisons which are qualitatively and quantitatively different pharmacologically. What the ultimate explanation of the phenomenon may be is not yet certain; however, it is certain that treatment of blood sera and drugs with roentgen rays of different wavelengths is of considerable diagnostic value in medical work and may be of therapeutic importance, as has already been established by our experiences with pemphigus and hemophilia. The present research, although it must still be re-

garded as of a preliminary and heuristic nature, certainly warrants further investigation along the above most interesting lines.

Finally it must be emphasized that the above experiments with roentgen rays were all carried on in the laboratory (with two exceptions) and at present cannot be applied clinically without further work. The two exceptions are the diseases pemphigus and hemophilia concerning which some favorable therapeutic results in patients have already been obtained.

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THIMBLE CHAMBER CALIBRATION ON SOFT ROENTGEN RAYS

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I. INTRODUCTION

THIMBLE chambers of the Victoreen type are normally designed for the measurement of relatively hard radiations and are customarily calibrated using roentgen-ray beams which are produced by tubes with an applied voltage of 70 to 200 kv., and which are subjected to some preliminary filtration; at least 2 mm. of alumimum or 0.2 mm. of copper. Over this range, the chambers yield readings which are practically independent of the radiation quality when calibrated against a free-air chamber. However, in the absence of any other ionization chamber, they are frequently used for measuring very much softer radiations than those for which they are designed or calibrated. Numerous cases have come to our attention where the red bakelite 25 r chamber has been employed to measure radiations produced by potentials as low as 20 or 30 kv., and it has been obvious in many cases that the users have had no reasonable idea as to the magnitude of the errors* involved. It therefore appeared to be desirable to investigate the magnitude of these errors and provide some quantitative data thereon.

Measurements cited in this paper with respect to the effect of added filtration on the calibration relate primarily to one 25 r chamber. The effect of thimble chamber type is studied using red bakelite 25 r, 100 r, and 250 r chambers, as well as the newly designed 250 r nylon chamber. When calibrations are made in a given roentgen-ray beam, or in different beams of exactly the same quality, then, as noted below, different chambers of the same type generally require the same corrections.† Similarly, chambers of different types require different corrections.

While our results may be taken as typical, the very magnitude of the corrections required indicates that whenever a thimble chamber is to be used for precise measurement in the very soft roentgen-ray region, it should be specifically calibrated for the exact conditions under which it will be used. This becomes the more important, the lower the roentgen-ray excitation potential. The wave form of the excitation potential becomes increasingly more important at the lower potentials also.

It is desirable for thimble chamber readings to bear a constant relationship to those of a standard free-air chamber over a wide range of roentgen-ray quality. To achieve this, it is necessary that the type of absorption and scattering in the thimble chamber wall be equivalent to that which is observed in air, and, that the absorption in the wall thickness be negligible in comparison with the transmission through it, or, that the secondary corpuscular radiation within the cavity be enhanced by means of a suitable internal coating of the wall to compensate for radiation lost by absorption in the wall thickness.

The practical attainment of this requirement is not difficult for 50 to 200 kv. roentgen rays emitted by a tube whose inherent filtration is at least 0.2 mm. of copper. For example, in the measurement of radiation from such a tube, the Victoreen 25 r thimble chamber, with its 0.6 mm. red bakelite wall, reads only 5 per cent low for 50 kv. radiation if it reads correctly for 100 to 200 kv. radiation.

The problem is much more difficult, how-

* By "error" is meant the departure of r-meter readings from those of a standard free-air chamber.

† "Correction," as here used, is a factor by which r-meter readings must be multiplied to make them agree with those of a standard free-air chamber.

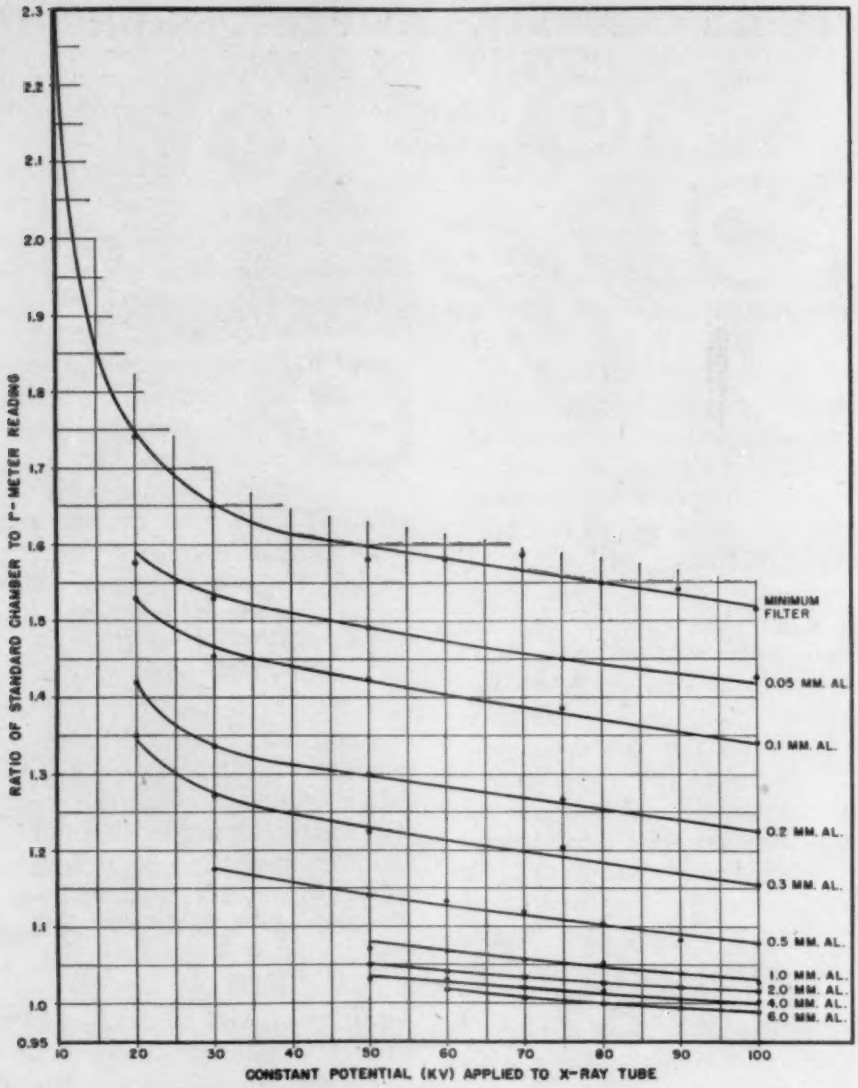

FIG. 1. The effect of roentgen-ray excitation potential and added aluminum filtration upon corrections required to the readings of a 25 r bakelite thimble chamber on r-meter No. 1193 when calibrated on roentgen rays generated by a tube with 1.5 mm. of beryllium inherent filtration.

ever, in the case of long wavelength roentgen rays, produced by a tube whose inherent filtration is, say, 1.5 mm. of beryllium. Roentgen rays as long as 4 Ångströms in wavelength are available in measurable quantity from such a tube, and these are readily absorbed, even in a few centimeters of air. There are applications where it is necessary to determine the exposure at or near the portal of a beryllium window tube. A properly designed chamber, therefore, should measure 4 Ångström roentgen rays (approximately 3 kv. quality), with a minimum of correction.

An attempt has been made in this direction,[1] utilizing an ionization chamber having a beryllium wall. The use of an open-air chamber has been reported,[2] utilizing a limiting diaphragm and a mesh type electrode system consisting of silk threads soaked in india ink to make them electrically conducting. A similar chamber has also been constructed,[3] substituting, in place of the mesh of silk threads, Kodapak

I, which is cellulose acetate sheet 0.00088 inch thick containing some plasticizer. Its calibration at the National Bureau of Standards yields scale factors (roentgens per scale division) which vary by less than 8 per cent as the roentgen-ray excitation potential is varied from 7.5 to 90 kv. and stances, 100 cm. of air at approximately 760 mm. of Hg pressure and 22° centigrade. It is necessarily a part of the minimum filtration, although it is not hereinafter so designated.

The standard ionization chamber used in in this comparison was the one designed for

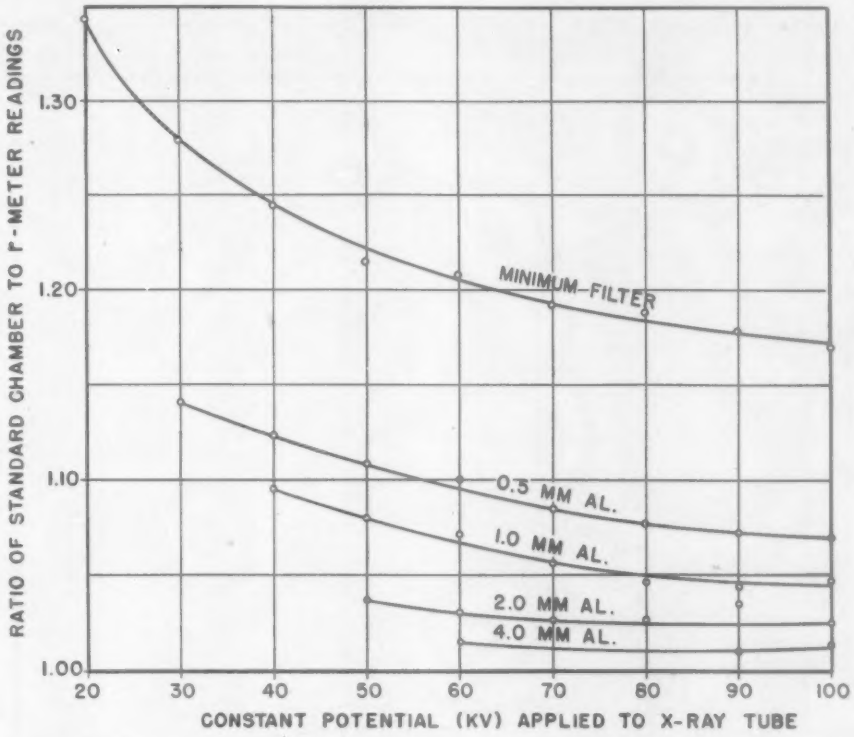

FIG. 2. The effect of roentgen-ray excitation potential and added aluminum filtration upon corrections required to the readings of a 25 r bakelite thimble chamber on r-meter No. 1193 when calibrated on roentgen rays generated by a tube with 1.3 mm. of cerium glass inherent filtration.

the filtration from the minimum of 1.5 mm. of beryllium plus 100 cm. of air to this plus 4 mm. of alumimum.

II. EXPERIMENTAL PROCEDURE AND RESULTS

In this study, the usual substitution method was employed in the calibration of the thimble chambers, the radiation being first measured with a standard guarded field, free-air ionization chamber and then with the thimble chambers placed in the position of the limiting diaphragm. The filtration between the roentgen-ray tube portal and the ionization chamber is, in all in-measuring radiations produced by potentials up to 200 kv. It has an air path of 21.1 cm. between the limiting diaphragm and the front edge of the collector plate.[4] Corrections required for the air absorption over this distance vary from about 0.5 per cent for 200 kv. radiation to 33 per cent for 10 kv. radiation[5] and these have been applied in this calibration.

"Constant"* potentials varied in steps between 10 and 200 kv. were employed on each of two tungsten target roentgen-ray

* The power supply has a resistance-capacitance filter to reduce the ripple to 0.05 per cent per milliampere current drain, and currents used in these calibrations did not exceed 10 milliamperes.

tubes used in the calibration. The first was a thin-walled (1.3 mm.) cerium-glass tube, which offers about as little inherent filtration as any glass-window tube. The second was a 200 kv. water-cooled tube whose window thickness is only 1.5 mm. of beryllium, and which has almost no inherent filtration.

The r-meter readings were observed over approximately the same scale range to avoid any possible scale factor error, and were readily reproduced within ± 1 per cent. This is an over-all error, which includes fluctuations in the calibrating equipment of not greater than ±0.3 per cent.

Figure 1 shows thimble chamber corrections using the beryllium-window tube over the range of 10 to 100 kv., and for filtrations ranging from the minimum of 1.5 mm. of beryllium to this plus 6 mm. of aluminum of added filtration. For example, it is observed for the minimum filtration that the correction is 1.52 at 100 kv. and increases to 2.3 at 10 kv. It is obvious that with such a large correction, the calibration of a thimble chamber for use with very soft radiations must be made with considerable care. In fact some earlier studies[6] indicate the necessity of effecting a special calibration for each specific tube in conjunction with its own specific potential source. The addition of as little as 1 mm. of aluminum to the beam, however, reduces the error from 52 to 3 per cent at 100 kv. and from 60 to 8 per cent at 50 kv.

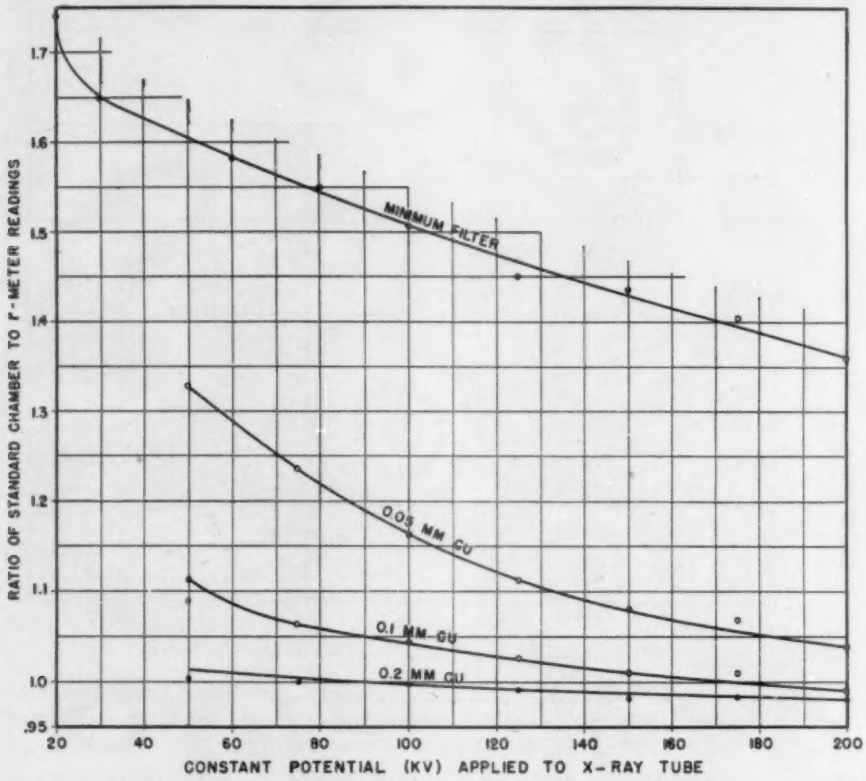

Fig. 3. The effect of roentgen-ray excitation potential and added copper filtration upon corrections required to the readings of a 25 r bakelite thimble chamber on r-meter No. 1193 when calibrated on roentgen rays generated by a tube with 1.5 mm. of beryllium inherent filtration.

Similar corrections using the 1.3 mm. glass-wall tube are shown in Figure 2. Here, for minimum filtration, it is seen that the correction varies from 1.17 at 100 kv. to 1.34 at 20 kv. Comparing these correc-

tions with those of the 0.3 mm. aluminum curve in Figure 1, it is found that they are closely alike over the whole potential range, indicating that the 1.3 mm. of cerium glass is equivalent in absorption to approximately 0.3 mm. of aluminum.

Calibration curves for the beryllium-window tube and copper filtrations at potentials up to 200 kv. are shown in Figure 3. It is observed that until approximately 0.22 mm. of copper filtration is added to the beam, the errors at low potentials are relatively large, 11 per cent, for example, at 50 kv. and 0.11 mm. of copper filtration. However, for 0.22 mm. of copper filtration, the thimble chamber agrees with the standard within ±2 per cent over the range of 50 to 200 kv., and additional filtration does not change the calibration curves observably.

In Figure 4, calibration curves for roentgen rays from the tube with 1.5 mm. of beryllium inherent filtration, and no added filtration, show the effect of thimble chamber type. In this comparison, three types of bakelite chambers (250 r, 100 r, and 25 r) were used in conjunction with r-meter, serial No. 1193. Another 25 r bakelite chamber was used in conjunction with r-meter, serial No. 1282. The readings of the two 25 r chambers and r-meters are the same, within experimental error, while those of the 100 r and 250 r chambers show substantially greater departure from those

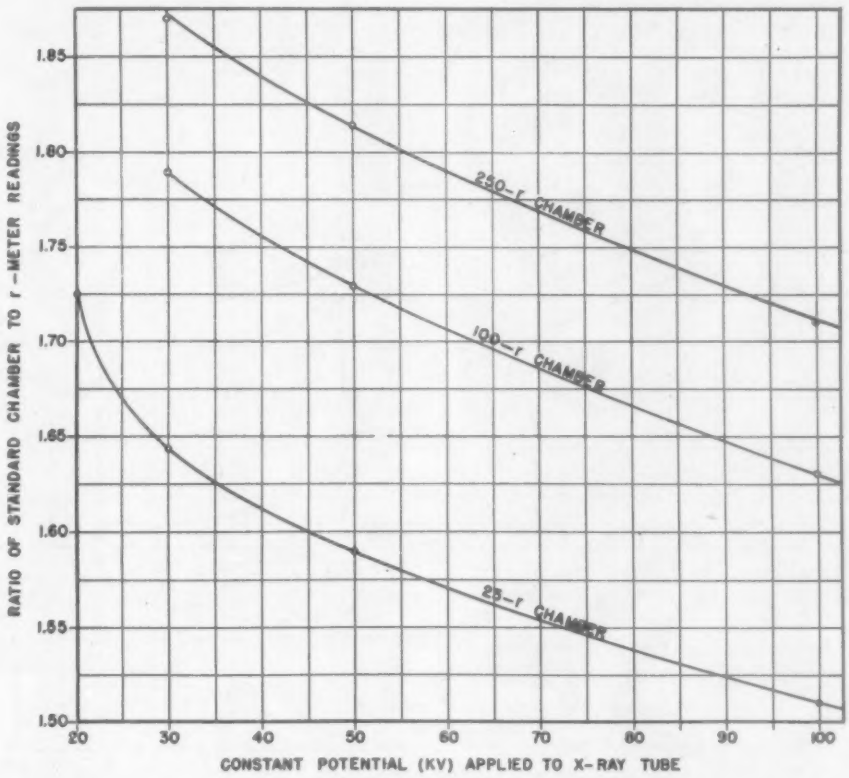

Fig. 4. The effect of roentgen-ray excitation potential upon the corrections required to the readings of different types of bakelite thimble chambers when calibrated on roentgen rays generated by a tube with 1.5 mm. of beryllium inherent filtration and no added filtration.

Note: The 250 r, 100 r, and 25 r chambers are each used in conjunction with r-meter No. 1193. Another 25 r chamber used in conjunction with r-meter No. 1282 yields readings which are the same within experimental error as those observed with the 25 r chamber which were read on r-meter No. 1193.

of the standard chamber. It is interesting to note that the calibration curves for these chambers run closely parallel to each other. For example, the correction factor to the 100 r and 250 r chambers are 1.63 and 1.71, respectively, at 100 kv., and 1.79 and 1.87, respectively, at 30 kv., or differences of 0.08 at each potential.

A 250 r nylon chamber with a 0.005 inch wall thickness has recently become commercially available, and its calibration is shown in Figure 5 using a roentgen-ray tube with 1.5 mm. of beryllium inherent filtration. For minimum-filtered radiation this chamber reads in error by 31.5 to 28 per cent over the range of 30 to 100 kv. This is in contrast with an error in the 250 r red bakelite chamber readings of 87 to 71 per cent in the same excitation potential range, as seen in Figure 4.

Table 1 shows the aluminum half-value layers for 10 to 200 kv. roentgen rays with filtration ranging from 1.5 mm. of beryllium to this plus 6 mm. of aluminum. For minimum filter the very very small half-value layers, even at 200 kv. indicate that the great part of the absorbed radiation is extremely soft, perhaps in the region of 20 to 30 kv., in terms of the usual measuring techniques. As an example of the effect of roentgen-ray beam quality upon thimble chamber calibration, it is observed in Figure 5 that 6 mm. of aluminum is required to reduce the correction factor to a minimum at 150 kv. Table 1 indicates that a 150 kv. beam, prefiltered by 6 mm. of aluminum, has a half-value layer of 7.6 mm. of aluminum. This is in contrast to half-value layers ranging from 0.04 to 0.18 mm. of aluminum at 10 and 200 kv., respective-

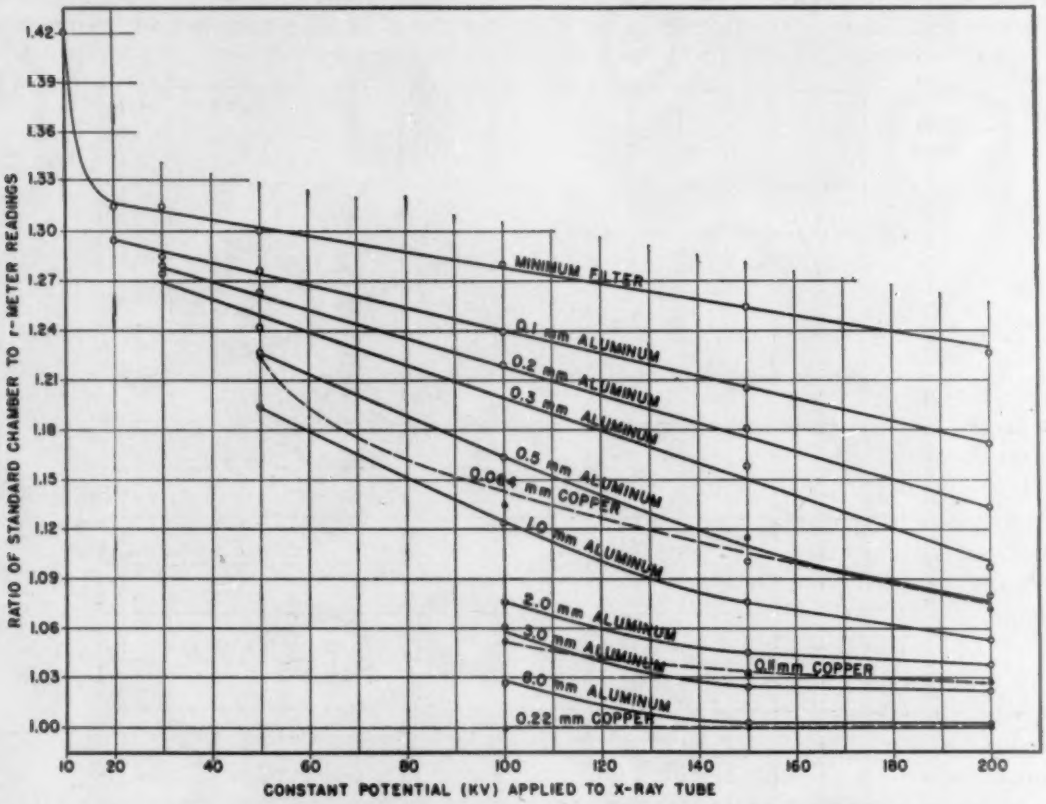

FIG. 5. The effect of roentgen-ray excitation potential and added aluminum and copper filtration upon corrections required to the readings of a 250 r nylon thimble chamber on r-meter No. 2449 when calibrated on roentgen rays generated by a tube with 1.5 mm. of beryllium inherent filtration.

TABLE I

ALUMINUM HALF-VALUE LAYER DETERMINED WITH FREE-AIR IONIZATION CHAMBER AS A FUNCTION OF FILTRATION AND OF ROENTGEN-RAY EXCITATION POTENTIAL

Constant Potential	Half-Value Layer of Aluminum								
	Minimum Filter*	Added Filter							
		0.1 mm. Al	0.2 mm. Al	0.3 mm. Al	0.5 mm. Al	1.0 mm. Al	2.0 mm. Al	3.0 mm. Al	6.0 mm. Al
(kv.)	(mm.)	(mm.)	(mm.)	(mm.)	(mm.)	(mm.)	(mm.)	(mm.)	(mm.)
10	0.04	0.06	0.10						
20	0.08	0.11	0.15	0.18	0.22				
30	0.09	0.14	0.19	0.27	0.35	0.6	0.9	1.2	
50	0.10	0.15	0.29	0.34	0.57	1.0	1.4	1.9	2.8
100	0.11	0.19	0.37	0.48	1.0	1.8	2.9	3.6	5.3
150	0.14	0.29	0.64	1.2	2.0	3.2	4.6	5.5	7.6
200	0.18	0.40	1.3	2.1	3.4	4.6	6.3	7.1	8.8

* 1.5 mm. of beryllium plus 100 cm. of air.

for minimum filtered beams. In view of the large percentages of soft components in beams from beryllium-window tubes, it is to be expected that chambers used for measuring radiations from such tubes, with no added filtration will be very critical as to design characteristics.

III. CONCLUSION

Thimble chambers can be calibrated for use with the very low potential, lightly filtered radiations, such as produced by beryllium-window roentgen-ray tubes. However, the errors may be as large as 130 per cent for radiation produced at 10 kv. constant potential.

Considerable care must be exercised in determining the amount and kind of filtration and potential employed in thimble chamber calibrations for soft roentgen rays. These factors are relatively unimportant, however, where filtrations above 0.2 mm. of copper or about 6 mm. of aluminum are used.

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X-ray Section
National Bureau of Standards
Washington, D. C.

A NEGATIVE FEEDBACK DOSAGE RATE METER USING A VERY SMALL IONIZATION CHAMBER

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DURING the past few years several types of devices for measuring the radiation at a point have been described in the literature. Condenser chambers of very small physical dimensions have been developed.[1,7,9,10] These are especially useful for measuring the dose received at points within body cavities or even in the tissue surrounding radium implants. These chambers can be charged conveniently and subsequently measured by using an electrometer device developed by Spiers and Hay.[8] They are not particularly suited to the measurement of radiation at a large number of points within a phantom since the time taken to charge the chamber, place it in position, expose the chamber and finally measure the charge remaining on it can become appreciable. For such work a negative feedback direct current amplifier is useful.

Several amplifiers of this type have been described in the literature.[2,3,5] These devices all amplify and measure the small ionization current in an associated thimble chamber and so yield an instantaneous reading of the intensity of the roentgen-ray beam. If depth dose data are required such a chamber can be moved through a phantom while the intensity of the roentgen-ray beam is held constant. Devices using two thimble chambers have been developed[4] which avoid the need of holding the output of the roentgen machine constant. Most of these amplifiers require a rather large thimble chamber in order to obtain an ionization current large enough for amplification. This means of course that the intensity of radiation at a "point" cannot be measured. In this respect such devices are not as useful as the small condenser chamber.

In order to overcome this difficulty the authors have developed a highly sensitive D. C. amplifier using a very small ionization chamber. It cannot be claimed that this device is simple in nature but it does serve as a useful tool in a radio therapy department for measuring backscatter and depth dose and for the investigation of stray radiation about treatment cones. It will be used for the investigation of the depth dose obtainable with the 25 mev. betatron installed at the University of Saskatchewan. It has been in routine operation for about one year and has been found to be reliable in operation. The D.C. amplifier is capable of measuring currents down to 10^{-14} amperes, and in conjunction with an ionization chamber of 50 mm.^{3} volume has been used to measure radiation intensities of 5 r/min. to 500 r/min. with an accuracy of 1 per cent. For the higher dosage rates a chamber with a volume of 5 mm.^{3} has been used successfully. A photograph of the amplifier and a selection of the probes which have been used with it are shown in Figure 1. The 0–100 microammeter in the upper right hand corner is the meter on which the intensity of the roentgen-ray beam striking the thimble chamber is measured. The parts of the radiation meter will be described in turn.

The Probe. It is desirable to locate the thimble chamber near the electrometer tube to eliminate the effects of radiation on the sensitive electrode and to keep the time constant of the device small. The original probe *A* (Fig. 1) was made made as a unit but all the others shown in Figure 1 were constructed so that a selection of thimble chambers could be connected to the probe by means of a screw fitting. This greatly increases the usefulness of the device for

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thimble chambers with special properties can be employed at will. In order to keep the probe small in volume the VX-41 tube manufactured by the Victoreen Instrument Company was used as the electrometer tube. It has a volume of about 1 cm.^{3} and excellent electrical characteristics, its input resistance when used in the space charge grid connection being about 10^{16} ohms. The electrical connections for the probe are shown in Figure 2.

It will be seen that the thimble chamber is connected so that the outer sheath is at ground potential while the sensitive central electrode is about 15 volts negative with respect to ground and connected to the space charge grid of the VX-41. The normal operating voltages of the VX-41 measured with respect to the filament are indicated. When radiation falls on the thimble chamber the ionization current which flows through the 10^{11} ohm resistor would cause a change ΔV in the potential of the point Q if the point P were at a fixed potential. However, the point P is connected to the output of the amplifier in such a way that it changes in potential by $-\Delta V$ of approximately the same magnitude so that the potential of Q remains almost constant regardless of the ionization current. This negative feedback characteristic of the amplifier makes the device linear in operation and insensitive to changes in the characteristics of the tube. It is important that an electrometer tube never be operated with the plate voltage applied before the filament is at operating temperature. Otherwise the tube becomes destabilized and will show very serious zero drift until it has been operated for several hours. For this reason a switch S is placed in the plate circuit of the VX-41. The parts of the electrometer cir-

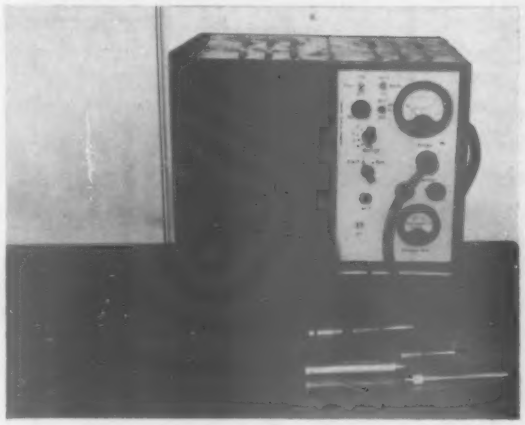

Fig. 1. Photograph of D.C. amplifier and probes.

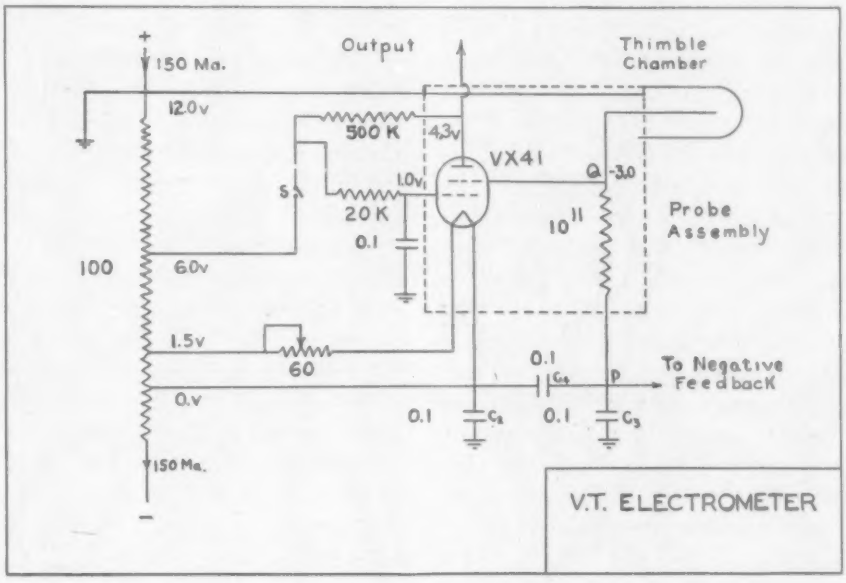

Fig. 2. Circuit diagram of vacuum tube electrometer circuit.

cuit which are situated in the probe are enclosed by the dotted line shown in Figure 2.

The actual mechanical construction of the probe is shown in Figure 3. The electrometer tube is located reasonably close to the ionization chamber and will at times be exposed to radiation. It is therefore necessary that the probe assembly be not affected by the radiation. Pockets of air trapped near the grid lead must be eliminated or the probe with a lead sheath 1/16 inch in thickness.

Power Supply and Amplifier. The power supply and amplifier shown diagrammatically in Figures 4 and 5 are based on a design originated by Miller.[6] Both circuits make use of the cathode control amplifier in tubes T_5 and T_6 of Figure 4 and T_2 and T_3 of Figure 5, for the elimination of cathode drift. One section of the twin triode

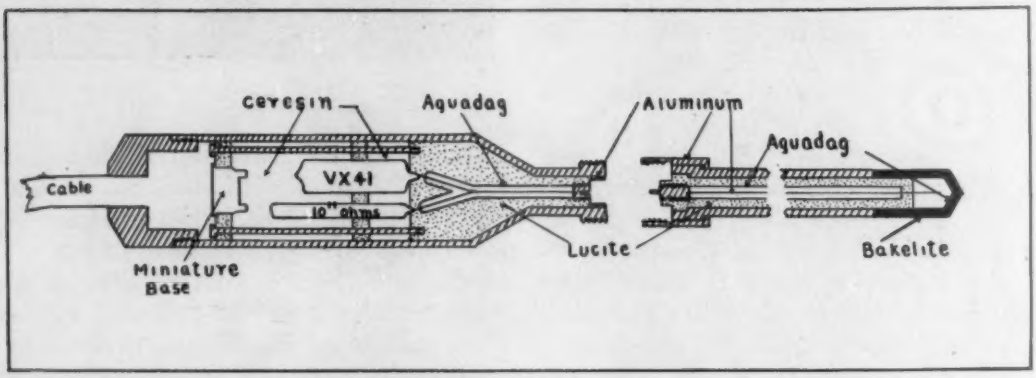

FIG. 3. Diagram of probe assembly.

enclosed in a field free region so that no ions can be collected. Therefore the grid lead is enclosed in a short piece of lucite tubing, coated with aquadag both inside and out, the outside surface being grounded and the inside connected to the grid. Ions produced in this region cannot be collected since they are in a field free region. The main volume of the probe is filled with ceresin wax of good insulating properties in order to exclude the air from around the tube and grid resistor. The probe without an ionization chamber was tested for radiation sensitivity using gamma rays, 400 kv. (peak) roentgen rays and 100 kv. (peak) roentgen rays. No deflection was observed for the gamma rays, a very small negative deflection when using 400 kv. (peak) roentgen rays and quite an appreciable deflection, using the softer roentgen rays. This effect is due likely to photoelectric emission from the grid of the VX-41. The effect was removed entirely by surrounding acts as the amplifier while the other section gives an inverse feedback, thus minimizing fluctuations due to changes in heater voltage, cathode emission, etc. Since a very accurately regulated power supply is necessary for the plate voltages of the tubes, it was decided to build one capable of operating the heaters of all critical tubes as well. For this reason the tube series which draws 150 milliamperes was chosen and the heaters of these tubes were placed in series with a bleeder chain (Fig. 2 and 5) from which voltages for the D. C. amplifier could be selected. The power supply of Figure 4 gives regulation to better than ± 1 millivolt for variations in the input voltage from 105 to 125 volts. This is quite adequate for the D. C. amplifier.

The signal from the VX-41 is amplified by tubes T_2 and T_3 (Fig. 5) and the amplified output is applied to one grid of the balanced cathode followers T_4 and T_5. The 0–100 output microammeter is connected

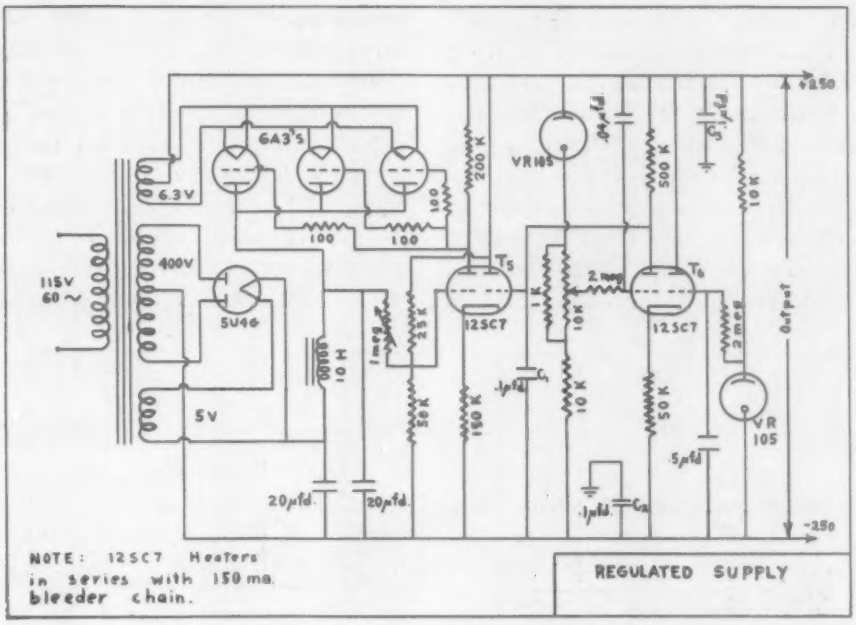

Fig. 4. Circuit diagram of regulated power supply for D. C. amplifier.

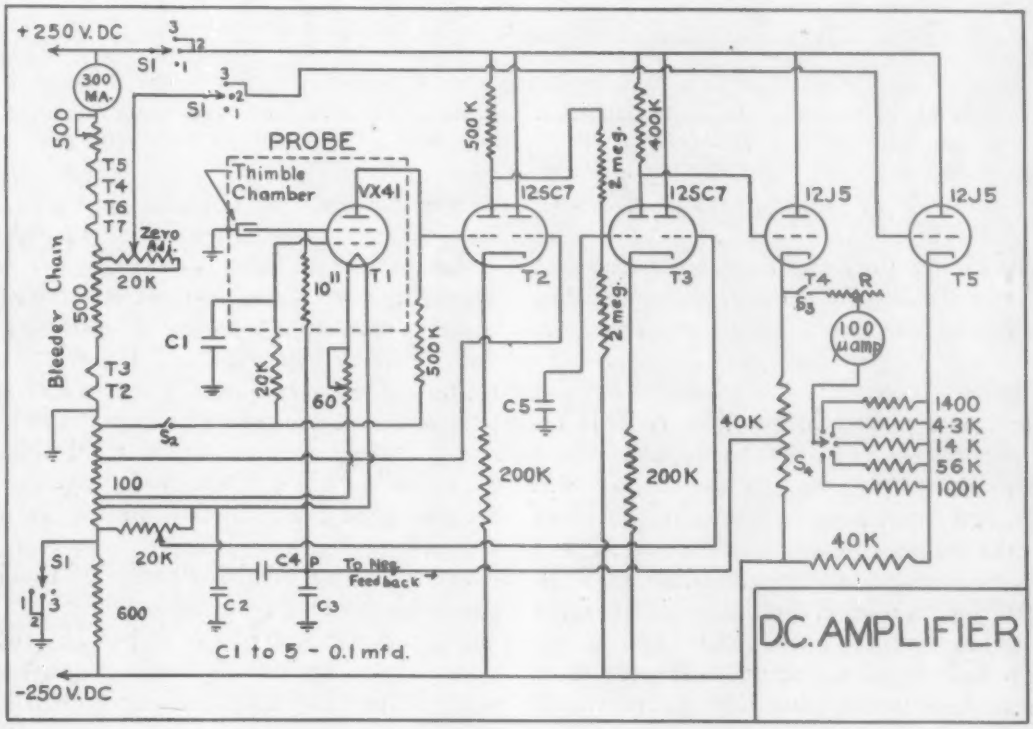

Fig. 5. Circuit diagram of D. C. amplifier.

between the cathodes of T_4 and T_5 through a rheostat R and range selector switch S_4. For zero ionization current the output meter is made to read zero by proper adjustment of the 20,000 ohm potentiometer to which the grid of T_5 is connected. Fifty per cent of the output from the cathode resistor of T_4 is fed back to the grid of the VX-41 so as to give negative feedback. Condensers C_2, C_3, C_4, and C_5 of Figure 5, and C_1, C_2, and C_3 of Figure 4 are necessary to ensure that negative feedback occurs for all frequencies. Without these troublesome oscillations occurred.

Before the power supply is turned on, S_1 (Fig. 5) is placed in position 1. This removes the section of the bleeder chain which supplies power to the VX-41 and removes the voltages from the plates of all the tubes in the amplifier. After the power supply starts to regulate as indicated by the small milliammeter (Fig. 1 and 5) S_1 may be moved through position 2 to 3. This applies voltage to the plates of the amplifier tubes and to the filament of the VX-41. After about one second, plate voltage may be applied to the VX-41 by closing S_2. Finally S_3 is closed and the zero adjustment made. After the radiation is turned on the proper range can be chosen by the selector switch S_4. For $R=0$, the five positions of S_4 give a full scale deflection for radiation intensities of about 5r/min., 15 r/min., 40 r/min., 100 r/min. and 300 r/min., respectively, using a thimble chamber of 50 mm.[3] Of course, other ranges can be obtained by placing different

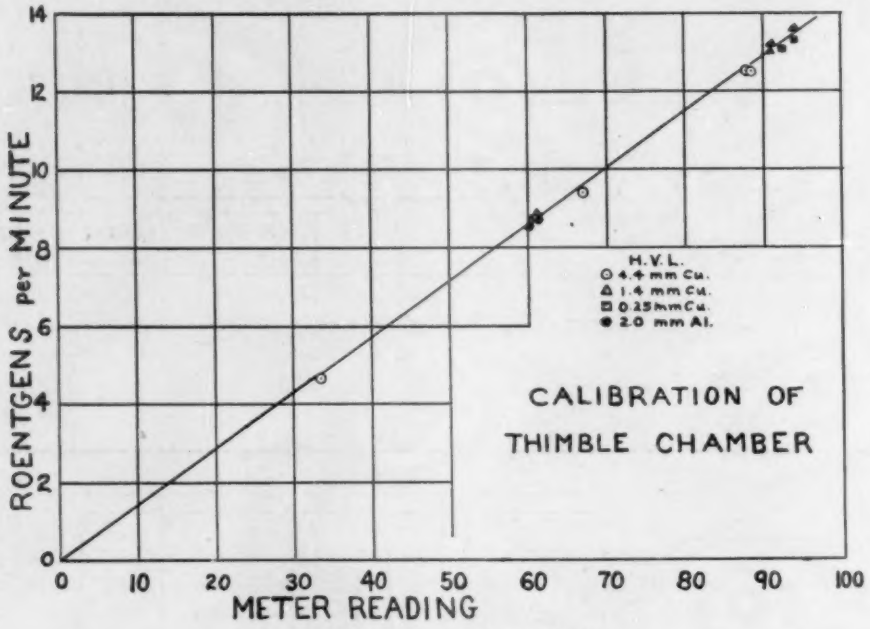

Fig. 6. Calibration of thimble chamber.

resistances in series with the meter. For depth dose work the variable resistance R is very convenient. Using it the output meter can be made to read 100 when the thimble chamber is at the surface of the phantom and the roentgen machine is giving a certain output. As the thimble is moved below the surface, percentage depth dose may be read directly off the output meter.

On the most sensitive range of the instrument erratic fluctuations amount to about 0.5 per cent of the full scale deflection. These are mainly due to thermal noise in the 10^{11} ohm resistor. When the amplifier is first turned on zero drift is troublesome but after about ten minutes

amounts to roughly 2 per cent per hour on the most sensitive range.

Linearity and Wavelength Dependence. Because of the large amount of negative feedback in the amplifier it would be expected that the instrument should be strictly linear. From examination of Table 1 and Figure 6 it will be seen that this is the case.

The wavelength dependence was checked against a Victoreen r-meter. The thimble chamber was constructed of red bakelite, coated on the inside with aquadag, and containing a central electrode of aluminum. By the proper choice of the size of central electrode it was possible to get a chamber which had the same response as the Victoreen. This is illustrated in Table 1 where the responses of the D.C. amplifier and the Victoreen are compared for four different qualities of radiation. The ratio of the readings on the two instruments, i.e. the sensitivity, is shown in the last two columns. It will be seen that for any one quality the sensitivity is constant regardless of the intensity of the radiation, indicating the linear response of the instrument. In the last column appear the average sensitivities for a given quality of radiation. This sensitivity varies somewhat with quality but the variation is hardly greater than the inherent error in the measurements would produce. The chamber has the same type of wavelength response as the Victoreen r-meter.

TABLE I

CALIBRATION OF THIMBLE CHAMBER

Half-Value Layer	D.C. Amplifier Reading R	Victoreen Reading r/min.	Sensitivity r/min/R	Average Sensitivity
	33.5	4.63	0.1405	
	67.0	9.41	0.1405	
4.4 mm. Cu	67.0	9.41	0.1405	0.1410
	88.0	12.45	0.1415	
	88.5	12.50	0.1415	
	60.5	8.70	0.1435	
	61.0	8.85	0.1450	
1.43 mm. Cu	91.0	13.2	0.1450	0.1442
	91.0	13.0	0.1430	
	94.0	13.6	0.1445	
0.25 mm. Cu	92.5	13.1	0.1420	0.1420
	94.0	13.3	0.1420	0.1420
2.0 mm. Al	60.0	8.57	0.1425	0.1422
	61.3	8.70	0.1420	

Uses of the Amplifier. The amplifier has been used for making depth dose measurements and measurements of backscatter. It has been found especially useful for investigating the distribution of radiation in a scattering medium in regions where the intensity of radiation changes rapidly. Because of the small size of the thimble chamber the device is particularly useful for this type of work. It is also useful for investigating stray radiation leaks about treatment cones. It is at present being used for the investigation of the depth doses obtainable with the 25 mev. betatron at the University of Saskatchewan. The results of these and other measurements will be reported later.

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Vol. 61, No. 4

DEPARTMENT OF TECHNIQUE

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ROENTGENOGRAPHIC FACSIMILE

A RAPID ACCURATE METHOD FOR REPRODUCING ROENTGENOGRAMS AT A DISTANCE VIA WIRE OR RADIO TRANSMISSION

By J. GERSHON-COHEN, M.D., *and* A. G. COOLEY
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THE roentgenologic service in hospitals of rural communities, in military outposts and in isolated mining and farming centers can seldom be arranged satisfactorily because the full-time attendance of a competent radiologist is not practical. These situations are now circumvented by obtaining the part time services of a radiologist in a nearby large community. By the use of roentgenographic facsimile, the full advantage of an experienced roentgenologist can be obtained at all times, thus affording rapid roentgenologic consultation whenever needed, including emergencies.

Since January 15, 1948, roentgenographic facsimile has been used daily in successful routine operation between the Chester County Hospital, West Chester, Pennsylvania, and the senior author's private office in Philadelphia, Pennsylvania, 28 miles distant. Whenever Dr. G. W. Brown, a graduate fellow in radiology, now training at the hospital, requires advice, he can transmit the facsimiles of the roentgenograms in question and, within a few

FIG. 1. The upright transmitter reveals the vertical glass drum on which is wrapped the roentgenogram. Inside this glass cylinder, an exciter lamp of the optical scanning system projects a beam of light through the glass and the enveloping film upon a photocell. Then through a special photocell circuit amplifier and synchronizing system, the signals are sent over commercial telephone circuits to the recorder similar to news-photo facsimile equipment. A special type of film is then exposed half the size of the original and quickly processed for interpretation.

minutes, engage in consultation with his senior, using the same telephone circuit over which the facsimiles were sent. Not only is this a valuable teaching aid, but it also quickly furnishes the patient's physician with an expert consultation and thus sustains his confidence in the over-all roentgenologic service. If a resident junior radiologist were not available, roentgenographic facsimile could be arranged so as to make possible direct quick consultation between the distant radiologist and the local referring physician. This has already been tried sufficiently to have established its practicality.

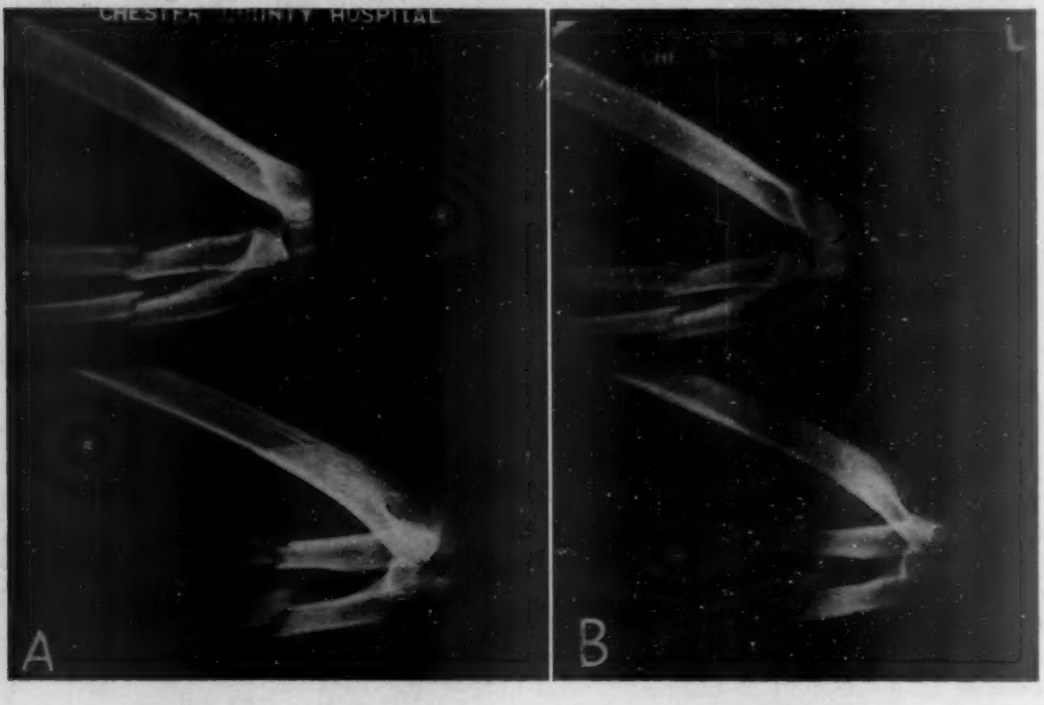

Fig. 2. *A*, fractures of bones of the forearm in original roentgenogram. *B*, facsimile of *A*.

The facsimile apparatus comprises a transmitter and a receiver. The roentgenogram to be copied is wrapped around a glass cylinder and held in place by an envelope of a simple clear plastic sheet. This cylinder rotates at 180 rpm. An optical scanning system projects a beam of light from an exciter lamp inside the cylinder through the wall of this glass cylinder and through the film onto a photoelectric cell. A special photocell circuit amplifier and synchronizing system is used, adopted from news-photo facsimile equipment now used by the newspapers and the Weather Bureau. The optical scanning system traverses the length of the drum so that 50 lines per inch are scanned. This enables transmission of a 14 by 17 inch film in slightly less than four minutes and smaller films in proportionately less time. The signals may be sent over telephone lines or radio circuits in the same way that wire photos or radio photos now are transmitted.

On the receiving apparatus, the negatives we use are half the size of the original roentgenograms. This recording film is of a type developed for wire-photo work by the Eastman Kodak Company and is known as E K Transmission Film, Type C. This film is easy to handle and it may be processed in ordinary solutions in about half the

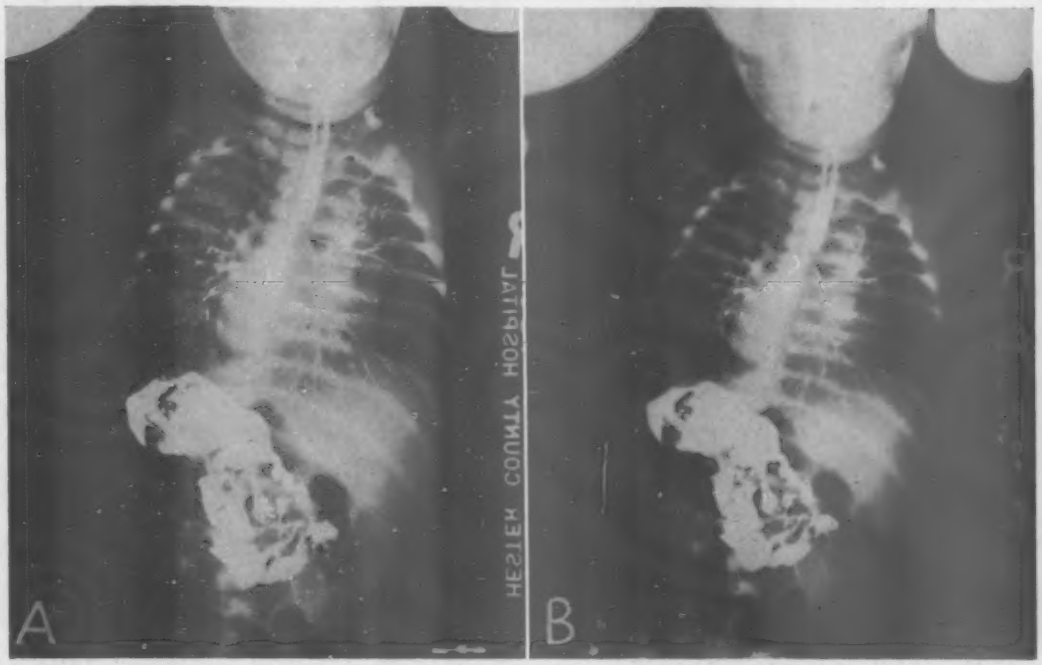

Fig. 5. *A*, lipiodol mapping of esophagus and tracheobronchial tree in case suspected of congenital defects in hypopharynx. No anatomical defects were found. *B*, facsimile of *A*.

time it takes to process regular roentgenograms. A very hot blast of air may be used for quick drying.

The facsimile retains all the detail of the original roentgenogi am. Because of the half-sized reduction of the facsimile, many details in it are sharper and more easily noticed than in the original film.

It is estimated that the cost of installation and operation of this equipment will be economically sound when it becomes available. During World War II, equipment having signal characteristics similar to this type of roentgenographic facsimile was used in regular service between Washington, D. C. and Anchorage, Alaska. Excellent results were also obtained by the Office of War Information operated radio circuits over great distances, one of them between Chungking, China and Los Angeles, California.

It now seems probable that there will soon be available roentgenographic facsimile equipment which should prove to be a great aid in the solution of the problem of roentgenologic service for rural hospitals and various types of civilian and military medical outposts.

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Thirty-first Annual Meeting: Ambassador Hotel, Atlantic City, N. J., June 5–7, 1949.

EDITORIAL

GASTRIC VASCULAR SHUNTS

BARCLAY, in one of his thought-stimulating talks before the Faculty of Radiologists,[1,2] called attention to a number of pitfalls in the history of roentgenological diagnosis. He analyzed some of the lessons which have been learned over these many years and with prophetic vision pointed out a road to the future. He recalled that from its very beginning the roentgen ray was used as a method of study of the pathologic, and as a result, the roentgenologist was always looking for the abnormal, failing to appreciate to the fullest extent that he was also observing the normal. Barclay expressed regret that the anatomist in the early days of the roentgen ray had not appreciated its value in application to the anatomical studies of the viscera in the normal living subject, and also that the schools of physiology failed to appreciate to the fullest the value of roentgenology as an aid in studying the gastrointestinal tract.

No one is perhaps better equipped than Barclay to have pointed out these glaring defects. He has throughout the years stood at the forefront of his profession and has contributed enormously to an elucidation of the pathological problems with which the roentgenologist has to deal. He has recently made brilliant contributions to anatomy and physiology in his studies of the renal circulation and more recently has reported his epoch-making studies on the gastric vascular shunts. Barclay has throughout the years championed the thought that the proper approach to a study of any pathologic state must be had through a proper understanding of the normal.

In a recent issue of the *British Journal of Radiology*, Barclay and Bentley[3] in a report of their studies on "The Visualisation of the Human Stomach: A Preliminary Note on the Shunting Effect of Trauma" have demonstrated anew the important lesson of the worthwhileness of intimate anatomical studies of the normal. In the course of their investigation into the blood vessels of the ulcerated stomach it became evident that the circulation through the gastric vessels is modified as a result of the conditions of the surgical operation. The mucous membrane of stomachs removed at operation is observed to be excluded from the active circulation in the stomach wall, further studies indicating that this is brought about by an arteriovenous shunt, similar to that described by Trueta and associates[4] in the kidney. As a result of their studies, Barclay and Bentley produced evidence of the existence of a system of arteriovenous anastomoses in the submucosa of the stomach wall, and they postulate that these shunts are probably under sympathetic control; their opening by nervous stress or trauma will deprive the mucosa of its vital blood stream.

In order that the arteries and their branches might be demonstrated down to the arterioles, a proprietary preparation of bismuth oxychloride ("Chlorbismol"), 20 per cent, was used as the contrast medium,

[1] Barclay, A. E. Radiology—empiricism or science? *Brit. J. Radiol.*, 1943, *16*, 344–347.

[2] Roentgenological problems, past and future. Editorial. Am. J. Roentgenol. & Rad. Therapy, 1944, *51*, 96–97.

[3] Barclay, A. E., and Bentley, F. H. The visualisation of the human stomach; a preliminary note on the shunting effect of trauma. *Brit. J. Radiol.*, Feb., 1949, *22*, 62–67; also *Gastroenterology*, Feb., 1949. Also, Gastric vascular shunts. *Lancet*, Feb. 12, 1949, *1*, 267–268.

[4] Trueta, J., Barclay, A. E., Daniel, P. M., Franklin, K. J., and Prichard, M. M. L. Studies on the Renal Circulation. Blackwell Scientific Publications, Ltd., Oxford, 1947.

injected into one of the gastric or gastro-epiploic arteries. This mass was chosen because it has a particle size too large to enter the capillaries, and it outlines the larger vessels perfectly. Such injection in the cadaver stomach shows that the larger arteries divide during their passage through the stomach wall to form a main plexus of smaller arteries lying in the submucous layer between the muscle coat and the mucosa, over the whole stomach wall. These anastomoses are of large size and are readily seen, and moreover they are so profuse that an injection through a single gastric or gastro-epiploic artery suffices to fill the whole vascular anastomotic plexus of both anterior and posterior stomach walls, and also the other gastric and gastro-epiploic arteries by retrograde injection.

They found that it was necessary to use an injection mass of smaller particle size in order to demonstrate the peripheral vascular supply. This consists of finer vessels arising from the main plexus. For this purpose colloidal silver iodide, 10 per cent, was used. The small arterioles and capillaries when filled with this contrast medium are seen quite clearly in micro-arteriographs. Cadaver preparations in which this mass was injected show that smaller vessels arise from the main plexus and run through the submucosa and the muscularis mucosae towards the under aspect of the mucous membrane, where they anastomose with each other to form an intricate plexus of finer vessels, close to the mucous membrane.

From this plexus arises a rich vascular network supplying the gastric mucosa, formed from large numbers of fine arterioles which then break up into capillaries. These vessels run perpendicularly through the mucosa toward the surface, and their appearance in a micro-arteriograph is very striking.

Barclay and Bentley observed that when the arteries of stomachs removed at operation were injected with colloidal silver iodide at the same pressure and using the same technique as in the cadaver, there was an important difference compared with the cadaver stomach. Whereas in the latter the vessels of the mucosa were filled over wide areas, in the operation specimens it was difficult to find an area of mucous membrane in which the injection mass had reached the peripheral circulation at all. While the technique of the injection was identical in the two varieties of stomachs, in no instance was it possible to outline the vessels of the mucosa, that is the peripheral circulation, in twelve specimens removed at operation except in occasional small and very inadequately filled areas.

The appearances obtained in these operation specimens suggested either that there was some impediment to the entry of the injection mass into the peripheral circulation in the mucosa in the operation specimens, or that the injection flowed from the arteries of the submucosal plexus directly into the gastric veins by some easier channel than that afforded by the mucosal network; in short, from this observation there appeared to be an arteriovenous anastomosis, or shunt, located in the submucous plexus.

The investigators thought that the conditions under which the stomachs were removed at operation would favor the action of any shunt, if one existed. Thus, opening of the peritoneal cavity to the air, manipulation of the stomach and traction on its mesenteries would all inflict a degree of trauma, while the application of clamps would then effectively cut off the nerve supply. From the observations gained from their work on the renal circulation, they thought that such a degree of stimulation might open up arteriovenous shunts reflexly, and the application of clamps would fix the peripheral vascular pattern in the shunted condition.

They thought that if such a shunt were to exist functionally, then it must be almost complete in its action to account for the practically total emptiness of the mucosal vessels. With this thought in mind, they made observations at six operations on the surface veins of the stomach from

the moment when the peritoneal cavity was opened, taking care that the oxygenation of the patient remained at a constant level. They observed that the veins coursing along the anterior wall of the stomach changed in color during the first two or three minutes after the peritoneum was opened, from purple-blue to a dusky pink. While this color change was occurring, samples of blood were taken from a venous tributary running toward the lesser curvature of the stomach as quickly as possible after the peritoneum was opened. A second sample was taken from an adjacent vein three minutes later when the color change was apparent. The blood was aspirated directly into potassium oxylate solution, and the percentage oxygen saturation of the hemoglobin determined by the method of Kramer. The percentage saturation of the first sample of blood removed was 74 per cent and of the second sample 91 per cent. Such a rapid change in oxygenation suggested strongly a direct passage of blood from the arterial to the venous side must have occurred through an arteriovenous shunt.

The investigators thought that if such a shunt is brought into play by opening the peritoneal cavity and trauma to the stomach, it should be possible to modify the shunt or to prevent its occurrence by blocking the sympathetic nerves to the stomach before the operation is begun. This thought was brought about by the fact that it is known from their work on the renal circulation that the arteriovenous anastomoses in the kidney are under the control of the autonomic nervous system.

In order to test the correctness of this postulate, a patient upon whom a gastrectomy was to be performed was anesthetized with a combination of general and high spinal anesthesia. The spinal anesthetic ascended to the level of the first and second thoracic vertebrae and the systolic pressure fell from 145/85 to between 80/40 and 40/? throughout the operation. The vessels of the excised stomach were injected with colloidal silver iodide in the usual way. The resulting micro-arteriograph showed a remarkable difference compared with all the other injected operation specimens. In this stomach the mucosal vessels were abundantly filled in all areas of the stomach wall that were reached by the injection, giving the appearance of complete filling of the mucosal vessels.

Blocking of the sympathetic outflow throughout the operation had been followed by an extensive circulation through the mucous membrane in marked contrast to the absence of circulation to these vessels when the sympathetic pathways were intact.

The investigators concluded from these observations that in the wall of the stomach there are arteriovenous anastomoses in the region of the submucous plexus of vessels, whose opening excludes active circulation through the vessels of the mucous membrane. They further concluded that when the peritoneal cavity is opened and the stomach handled at operation, the shunt comes into play, and this condition persists in the excised stomach wall after the operation. These observations are consistent and agree with those made by Trueta and associates that the vascular pattern of the shunts within the kidney persists after the supplying vessels have been clamped and the nerve supply cut off.

From these studies the investigators adduced evidence indicating that the arteriovenous anastomoses in the stomach wall are under the control of the autonomic nervous system, for when the sympathetic outflow to the stomach is blocked by means of a spinal anesthetic the shunts do not open, and injection of the stomach vessels reveals filling of the extensive blood supply of the mucous membrane.

All of this epoch-making work is made possible by Barclay's[5] brilliant technical achievement in his development of micro-arteriography for without this, such a dis-

[5] Barclay, A. E. Micro-arteriography. *Brit. J. Radiol.*, 1947, *20*, 394–404; also, Am. J. Roentgenol. & Rad. Therapy, 1948, *60*, 1–12.

covery would not have been possible.

This report of Barclay and Bentley is a "preliminary note" and obviously further studies must and will be made. But this latest contribution is a great tribute to Barclay's perseverance in the investigation of his first love, namely the normal. These epoch-making studies of Barclay and his associates were carried on in spite of Dr. Barclay's serious illness, and after fifty years of contribution to the progress of roentgenology, he makes observations on a study of the normal which have untold possibilities in elucidating some of the pathologic problems such as the sudden formation of peptic ulcers and the acute penetrating or perforating ulcers of the stomach and duodenum which are seen frequently. This brilliant work opens up great possibilities not only in explaining some of the causative factors in ulcer formation but may ultimately be of great benefit in the cure of gastric and duodenal ulcers.

Barclay in this outstanding contribution brings again to the fore his emphasis of a need of well equipped research departments in the universities closely allied with the departments of anatomy, physiology and clinical medicine, having access also to the department of radiology of the hospital. Barclay conceived such research institutes as an imperative need and in his opinion they should be staffed by men with clinical experience in roentgenologic work. Certainly his brilliant contributions in these later years have justified such a conception of a great research institute.

SOCIETY PROCEEDINGS, CORRESPONDENCE AND NEWS ITEMS

Items for this section solicited promptly after the events to which they refer

MEETINGS OF ROENTGEN SOCIETIES*

United States of America

American Roentgen Ray Society
Secretary, Dr. H. Dabney Kerr, University Hospital, Iowa City, Iowa. Annual meeting: Netherland Plaza Hotel, Cincinnati, Ohio, Oct. 4–7, 1949.

American Radium Society
Secretary, Dr. H. F. Hare, 605 Commonwealth Ave., Boston, Mass. Annual meeting: Ambassador Hotel, Atlantic City, N. J., June 5–7, 1949.

Radiological Society of North America
Secretary, Dr. D. S. Childs, 607 Medical Arts Bldg., Syracuse, N. Y. Annual meeting: 1949, to be announced.

American College of Radiology
Executive Secretary, William C. Stronach, 20 N. Wacker Drive, Chicago 6. Annual meeting: Chalfonte-Haddon Hall, Atlantic City, N. J., June 5, 1949.

Section on Radiology, American Medical Association
Secretary, Dr. U. V. Portmann, Cleveland Clinic, Cleveland, Ohio, Annual Meeting: Atlantic City, N. J., June 8–10, 1949.

Alabama Radiological Society
Secretary, Dr. W. W. Anderson, Tuscaloosa, Ala. Next meeting time and place of Alabama State Medical Association, Montgomery, Ala., April 19–21, 1949.

Arkansas Radiological Society
Secretary, Dr. Fred Hames, 511 National Bldg., Pine Bluff, Ark. Meets every three months and also at time and place of State Medical Association.

Brooklyn Roentgen Ray Society
Secretary, Dr. A. H. Levy, 1354 Carroll St., Brooklyn 13, N. Y. Meets monthly on fourth Tuesday, October to April.

Buffalo Radiological Society
Secretary, Dr. Mario C. Gian, 610 Niagara St., Buffalo, N. Y. Meets second Monday evening each month, October to May inclusive.

Central New York Roentgen Ray Society
Secretary, Dr. Dwight V. Needham, 608 E. Genesee St., Syracuse N. Y. Meets January, May, November.

Central Ohio Radiological Society
Secretary, Dr. Paul D. Meyer, Grant Hospital, Columbus, Ohio. Meets at 6:30 P.M. on second Thursday of October, December, February, April, and June at Seneca Hotel, Columbus, Ohio.

Chicago Roentgen Society
Secretary, Dr. John H. Gilmore, 720 N. Michigan Ave., Chicago 11, Ill. Meets second Thursday of each month October to April inclusive at the Palmer House.

Cincinnati Radiological Society
Secretary, Dr. Eugene L. Saenger, 735 Doctors Bldg., Cincinnati 2, Ohio. Meets last Monday of each month, September to May, inclusive.

Cleveland Radiological Society
Secretary, Dr. Merthyn A. Thomas, 10515 Carnegie Ave. Cleveland 6, Ohio. Meetings at 6:30 P.M. on fourth Monday of each month from October to April.

Colorado Radiological Society
Secretary, Dr. Mark S. Donovan, 306 Majestic Bldg., Denver 2, Colo. Meets third Friday of each month at Department of Radiology, Colorado School of Medicine.

Connecticut Valley Radiologic Society
Secretary, Dr. E. W. Godfrey, 1676 Boulevard, West Hartford, Conn. Meets second Friday of October and April.

Dallas-Fort Worth Roentgen Study Club
Secretary, Dr. X. R. Hyde, Medical Arts Bldg., Fort Worth, Texas. Meets in Dallas on odd months and in Fort Worth on even months, on third Monday, 7:30 P.M.

Detroit Roentgen Ray and Radium Society
Secretary, Dr. W. G. Belanger, Harper Hospital. Meets monthly on first Thursday from October to May, at Wayne County Medical Society Building.

East Bay Roentgen Society
Secretary, Dr. Dan Tucker, 434-30th St., Oakland 9, Calif. Meets first Thursday each month at Peralta Hospital, Oakland.

Florida Radiological Society
Secretary, Dr. F. K. Hurt, Riverside Hospital, Jacksonville, Fla. Meets twice annually, in the spring with the annual State Society meeting, and in the fall.

Georgia Radiological Society
Secretary, Dr. Robert Drane, DeRenne Apartments, Savannah, Ga. Meets in mid-winter and at annual meeting of Medical Association of Georgia in the spring.

Houston X-ray Club
Secretary, Dr. Curtis H. Burge, 3020 San Jacinto St., Houston 4, Texas. Meets fourth Monday each month.

Radiological Society of Kansas City
Secretary, Dr. Arthur B. Smith, 800 Argyle Bldg., Kansas City, Mo. Meets third Thursday of each month.

Illinois Radiological Society
Secretary, Dr. Wm. DeHollander, St. John's Hospital, Springfield, Ill. Meets three times a year.

Indiana Roentgen Society
Secretary, Dr. William M. Loehr, 712 Hume-Mansur Bldg., Indianapolis 4. Meets second Sunday in May.

Iowa X-Ray Club
Secretary, Dr. Arthur W. Erskine, 326 Higley Bldg., Cedar Rapids, Iowa. Luncheon and business meeting during annual session of Iowa State Medical Society. Special meetings by announcement.

Kansas Radiological Society
Secretary, Dr. Anthony F. Rossitto, Wichita Hospital, Wichita, Kan. Meets annually with State Medical Society.

Kentucky Radiological Society
Secretary, Dr. W. C. Martin, 321 W. Broadway, Louisville. Meets annually in Louisville on first Saturday in Apr.

Long Island Radiological Society
Secretary, Dr. Marcus Wiener, 1430-48th St., Brooklyn, N. Y. Meets Kings County Med. Soc. Bldg. monthly on fourth Thursday, October to May, 8:45 P.M.

Los Angeles Radiological Society
Secretary, Dr. Wybren Hiemstra, 1414 S. Hope St., Los Angeles 15, Calif. Meets second Wednesday each month at Los Angeles County Medical Assn. Building.

Louisiana Radiological Society
Secretary, Dr. J. R. Anderson, 1130 Louisiana Ave., Shreveport. Meets annually during Louisiana State Medical Society Meeting.

Louisville Radiological Society
Secretary, Dr. E. L. Pirkey, Louisville General Hospital, Louisville 2, Ky. Meets monthly on second Friday at Louisville General Hospital.

* Secretaries of societies not here listed are requested to send the necessary information to the Editor.

Michigan Association of Roentgenologists
Secretary, Dr. R. D. McDuff, 220 Genesee Bank Bldg., Flint 3, Mich.

Milwaukee Roentgen Ray Society
Secretary, Dr. C. A. H. Fortier, 231 W. Wisconsin Ave., Milwaukee, Wis. Meets monthly on second Monday at University Club.

Minnesota Radiological Society
Secretary, Dr. Chauncey N. Borman, 802 Medical Arts Bldg., Minneapolis 2, Minn. Two meetings yearly, one at time of Minnesota State Medical Association the other in the fall.

Nebraska Radiological Society
Secretary, Dr. Ralph C. Moore, Nebraska Methodist Hospital, Omaha 3, Nebr. Meets third Wednesday of each month, at 6 P.M. at either Omaha or Lincoln.

New England Roentgen Ray Society
Secretary, Dr. George Levene, Massachusetts Memorial Hospitals, Boston, Mass. Meets monthly on third Friday, Boston Medical Library.

New Hampshire Roentgen Ray Society
Secretary, Dr. A. C. Johnston, Elliott Community Hospital, Keene, N. H. Meets four to six times yearly.

New York Roentgen Society
Secretary, Dr. Ramsay Spillman, 115 East 61st St., New York City. Meets monthly on third Monday, New York Academy of Medicine, at 8:30 P.M.

North Carolina Radiological Society
Secretary, Dr. J. E. Hemphill, 323 Professional Bldg., Charlotte 2, N. C. Meets in May and October.

North Dakota Radiological Society
Secretary, Dr. C. O. Heilman, 807 Broadway, Fargo. Meetings held by announcement.

Northern California Radiological Club
Secretary, Dr. C. E. Grayson, Medico-Dental Bldg., Sacramento 14, Calif. Meets at dinner last Monday, every second month, except June, July and August.

Ohio State Radiological Society
Secretary, Dr. Carroll C. Dundon, 2065 Adelbert Road, Cleveland 6, Ohio.

Oklahoma State Radiological Society
Secretary, Dr. W. E. Brown, Tulsa, Okla. Three regular meetings annually.

Oregon Radiological Society
Secretary, Dr. Boyd Isenhart, 214 Medical Dental Bldg., Portland 5, Oregon. Meets monthly 2nd Wednesday, 8:00 P.M., Library of University of Oregon Medical School.

Orleans Parish Radiological Society
Secretary, Dr. Joseph V. Schlosser, Charity Hospital, New Orleans 13, La. Meets first Tuesday of each month.

Pacific Northwest Radiological Society
Secretary, Dr. S. J. Hawley, 1320 Madison St., Seattle 4, Wash. Meets annually in May.

Pacific Roentgen Society
Secretary, Dr. L. H. Garland, 450 Sutter St., San Francisco, Calif. Meets annually, during meeting of California Medical Association.

Pennsylvania Radiological Society
Secretary, Dr. J. M. Converse, 416 Pine St., Williamsport. Annual Meeting: May 20 and 21, 1949, Bedford Springs Hotel, Bedford, Pa.

Philadelphia Roentgen Ray Society
Secretary, Dr. Arthur Finkelstein, Graduate Hospital, 19th and Lombard St. Meets first Thursday each month October to May, at 8:00 P.M., in Thomson Hall, College of Physicians.

Pittsburgh Roentgen Society
Secretary, Dr. R. P. Meader, 4002 Jenkins Arcade Pittsburgh 22, Pa. Meets 6:30 P.M. at Webster Hall Hotel on second Wednesday each month, October to May inclusive.

Queens Roentgen Ray Society
Secretary, Dr. J. E. Goldstein, 88-29 163rd St., Jamaica 3, N. Y. Meets fourth Monday of each month except during the summer.

Radiological Section, Baltimore Medical Society
Secretary, Dr. Harry A. Miller, 2452 Eutaw Place, Baltimore. Meets third Tuesday each month, September to May.

Radiological Section, Connecticut Medical Society
Secretary, Dr. Robert M. Lowman, Grace-New Haven Community Hospital, New Haven 11. Meets bimonthly second Thursday, at place selected by Secretary.

Radiological Section, District of Columbia Medical Society
Secretary, Dr. A. A. J. Den, 1801 K St., N. W., Washington, D. C. Meets Medical Society Auditorium, third Thursday, January, March, May, October at 8:00 P.M.

Radiological Section, Southern Medical Association
Secretary, Dr. Roy G. Giles, Temple, Texas.

Radiological Society of New Jersey
Secretary, Dr. Raphael Pomeranz, 31 Lincoln Park, Newark, N. J. Meets annually at time and place of State Medical Society. Mid-year meetings at place chosen by president.

Rochester Roentgen Ray Society, Rochester, N. Y.
Secretary, Dr. Ralph E. Alexander, 101 Medical Arts Bldg. Meets monthly on third Monday from October to May, inclusive, 8 P.M. at Strong Memorial Hospital.

Rocky Mountain Radiological Society
Secretary, Dr. Maurice D. Frazer, 1037 Stuart Bldg., Lincoln, Nebr. Meets Denver, Colo., August 18, 19, 20, 1949.

St. Louis Society of Radiologists
Secretary, Dr. Edwin C. Ernst, Beaumont Medical Building, St. Louis, Mo. Meets fourth Wednesday of each month, except June, July, August, and September.

San Diego Roentgen Society
Secretary, Dr. R. F. Niehaus, 1831 Fourth Ave., San Diego, Calif. Meets monthly, first Wednesday at dinner.

Section on Radiology, California Medical Association
Secretary, Dr. D. R. MacColl, 2007 Wilshire Blvd., Los Angeles 5, Calif.

Section on Radiology, Illinois State Medical Society
Secretary, Dr. Harold L. Shinall, St. Joseph's Hospital, Bloomington, Ill.

Shreveport Radiological Club
Secretary, Dr. R. W. Cooper, Charity Hospital, Shreveport, La. Meets monthly on third Wednesday, at 7:30 P.M., September to May inclusive.

South Carolina X-Ray Society
Secretary, Dr. T. A. Pitts, Baptist Hospital, Columbia, S. C. Meets in Charleston on first Thursday in November, also at the time and place of South Carolina State Medical Association.

Tennessee Radiological Society
Secretary, Dr. J. M. Frère, 707 Walnut St., Chattanooga, Tenn. Meets annually at the time and place of the Tennessee State Medical Association.

Texas Radiological Society
Secretary, Dr. R. P. O'Bannon, 650 Fifth Ave., Fort Worth 4, Texas.

University of Michigan Department of Roentgenology Staff Meeting
Meets each Monday evening from September to June, at 7 P.M. at University Hospital.

University of Wisconsin Radiological Conference
Secretary, Dr. E. A. Pohle, 1300 University Ave., Madison, Wis. Meets first and third Thursdays 4:00 to 5:00 P.M., September to May inclusive. Room 203, Service Memorial Institute, 426 N. Charter St., Madison.

Utah State Radiological Society
Secretary, Dr. Angus K. Wilson, 343 S. Main St., Salt Lake City 1, Utah. Meets third Wednesday in September, November, January, March and May.

Virginia Radiological Society
Secretary, Dr. P. B. Parsons, Norfolk General Hospital, Norfolk, Va. Meets annually in October.

Washington State Radiological Society
Secretary, Dr. Homer V. Hartzell, 310 Stimson Bldg., Seattle 1, Wash. Meets fourth Monday each month, October through May, College Club, Seattle.

X-Ray Study Club of San Francisco
Secretary, Dr. Ivan J. Miller, 49 Fourth St., San Francisco 3. Meets monthly on third Thursday at 7:45 P.M., January to June at Lane Hall, Stanford University Hospital, and July to December at Langley Porter Clinic, University of California Hospital.

Cuba

Sociedad de Radiología y Fisioterapia de Cuba
President, Dr. J. Manuel Viamonte, Hospital Mercedes, Habana, Cuba. Meets monthly in Habana.

Mexico

Sociedad Mexicana de Radiologia y Fisioterapia
General Secretary, Dr. D. P. Cossio, Marsella No. 11, Mexico, D. F. Meets first Monday of each month.

British Empire

British Institute of Radiology Incorporated with the Röntgen Society
Ordinary meeting, on the Thursday preceding the third Friday, October to May at 8:15 P.M.
Medical Members' meeting, on third Friday in each month at 5:00 P.M., 32 Welbeck St., London, W 1.

Faculty of Radiologists
Honorary Secretary, Dr. J. F. Bromley, 45, Lincoln's Inn Fields, London, W.C.2, England.

Section of Radiology of the Royal Society of Medicine (Confined to Medical Members)
Meets third Friday each month at 4:45 P.M. at the Royal Society of Medicine, 1 Wimpole St., London.

Canadian Association of Radiologists
Honorary Secretary, Dr. E. M. Crawford, 2100 Marlowe Ave., Montreal 28, Que. Meetings January and June.

Section of Radiology, Canadian Medical Association
Secretary, Dr. C. M. Jones, Inglis St., Ext. Halifax, N. S.

Société Canadienne-Francaise d'Electrologie et de Radiologie Médicales
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Western Australia, Dr. A. M. Nelson, 179-B St. Georges Terrace, Perth.
New Zealand, Dr. E. G. Lynch, 12 Bolton St., Wellington.

South America

Sociedad Argentina de Radiologia
Secretary, Dr. Guido Gotta, Buenos Aires, Argentina. Meetings are held monthly.

Sociedade Brasileira de Radiologia Medica
Secretary, Dr. Nicola Caminha, Av. Mem de Sa, Rio de Janeiro, Brazil. Meets monthly, except during January, February and March.

Sociedade Brasileira de Radioterapia
Secretary, Dr. Andrelino Amaral, Av. Brigadeiro Luiz Antonio, 644, São Paulo, Brazil. Meets monthly on second Tuesday at 9 P.M. in São Paulo at Av. Brigadeiro Luiz Antonio, 644.

Sociedad Peruana de Radiologia
Secretary, Dr. Julio Bedoya Paredes, Apartado, 2306, Lima, Peru. Meets monthly except during January, February and March, at Asociación Médica Peruana "Daniel A. Carrión," Villalta, 218, Lima.

Sociedad de Radiologica, Cancerologia y Fisica Medica del Uruguay
Secretary, Dr. Arias Bellini.

Continental Europe

Société Belge de Radiologie
General Secretary, Dr. S. Masy, 111 Avenue des Alliés, Louvain, Belgium. Meets monthly, second Sunday at Maison des Médecins, Brussels.

Ceskoslovenská společnost pro röntgenologii a radiologii v Praze
Secretary, Dr. Roman Bláha, Praha XII, stát. nemocnice, Czechoslovakia. Meets monthly except during July, August, and September. Annual general meeting.

Polish Society of Radiology
Secretary, Dr. L. Zgliczynski, 59 Nowogrodzka St., Warsaw, Poland. Next meeting, Krakow, June 2 and 3, 1949.

Gdansk Section, Polish Society of Radiology
Secretary, Dr. A. Smigielska, Akademia Lekarska, Gdansk. Meets monthly last Sunday at 10.30, X-Ray Dept., Akademia Gdansk.

Warsaw Section, Polish Society of Radiology
Secretary, Dr. L. Zgliczynski, 59 Nowogrodzka St., Warsaw, Poland. Meets monthly.

Societatea Romana de Radiologie si Electrologie
Secretary, Dr. Oscar Meller, Str. Banual Mărăcine, 30, S. I., Bucuresti, Roumania. Meets second Monday in every month with the exception of July and August.

All-Russian Roentgen Ray Association, Leningrad.
USSR in the State Institute of Roentgenology and Radiology, 6 Roentgen St.
Secretaries, Drs. S. A. Reinberg and S. G. Simonson. Meets annually.

Leningrad Roentgen Ray Society
Secretaries, Drs. S. G. Simonson and G. A. Gusterin. Meets monthly, first Monday at 8 o'clock, State Institute of Roentgenology and Radiology, Leningrad.

Moscow Roentgen Ray Society
Secretaries, Drs. L. L. Holst, A. W. Ssamygin and S. T. Konobejevsky. Meets monthly, first Monday, 8 P.M.

Scandinavian Roentgen Societies
The Scandinavian roentgen societies have formed a joint association called the Northern Association for Medical Radiology, meeting every second year in the different countries belonging to the Association.

Sociedad Espanola de Radiologia y Electrologia
Secretary, Dr. J. Martin-Crespo, Fuencarral, 7. Madrid, Spain. Meets monthly in Madrid.

Schweizerische Röntgen-Gesellschaft (Société Suisse de Radiologie)
President, Dr. H. E. Walther, Gloriastr. 14, Zürich, Switzerland.

Societa Italiana di Radiologia Medica
Secretary, Prof. Mario Ponzio, Ospedale Mauriziano Torino, Italy. Meets biannually.

PRELIMINARY PROGRAM

American Radium Society

THE following is the preliminary program which has been arranged for the Thirty-first Annual Meeting of the American Radium Society to be held at the Ambassador Hotel, Atlantic City, New Jersey, Sunday, Monday and Tuesday, June 5, 6 and 7, 1949.

Sunday Morning, June 5, 1949

1. Lay Propaganda. Affirmative—Charles Cameron, M.D., New York, N. Y. Negative—Daniel Blain, M.D. (by invitation), Washington, D. C.
2. State Control of Cancer. Herman Hilleboe, M.D., and M. L. Levin, M. D. (both by invitation), Albany, N. Y.
3. Federal Cancer Control Activities. Austin V. Deibert, M.D. (by invitation), Washington, D. C.

Monday Morning, June 6, 1949

1. Presidential Address. Maurice Lenz, M.D., New York, N. Y.
2. Planning the Radioisotope Program in the Hospital. Edith H. Quimby, D. Sc., and Carl Braestrup (by invitation), New York, N. Y.
3. Radioactive Colloidal Gold. Alfred I. Sherman, M.D. (by invitation), St. Louis, Mo., and James Nolan, M.D., Los Angeles, Calif.
4. Beta Radiation in Superficial Lesions of the Eye. Charles Iliff, M.D. (by invitation), Baltimore, Md.
5. Roles of Surgery and Radiation in the Treatment of Cancer. L. H. Garland, M.D. (by invitation), San Francisco, Calif.

Monday Afternoon, June 6, 1949

1. Cancer of the Lung. John Pool, M.D., New York, N. Y.
2. Primary Cancer of the Vagina. Robert E. Fricke, M.D., H. H. Bowing, M.D., and D. G. Decker, M.D. (by invitation), Rochester, Minn.
3. The Planning of Irradiation in Cancer of the Uterus and Cervix. Gilbert Fletcher, M.D. (by invitation), Houston, Texas.
4. Individualized Interstitial Irradiation of Carcinoma of the Uterine Cervix Using Cobalt^{60} in Needles Inserted through Lucite Templates: A Progress Report. Joseph L. Morton, M.D., Allan C. Barnes, M.D., and George W. Callendine, M.D. (all by invitation), Columbus, Ohio.

Janeway Lecture. Low Intensity of Radiation Element Needles. Charles L. Martin, M.D., Dallas, Texas.

Tuesday Morning, June 7, 1949

1. Endocrine Therapy in Breast Cancer. Roy Hertz, M.D. (by invitation), Washington, D. C.
2. Cancer of the Thyroid. Hugh F. Hare, M.D., Boston, Mass.
3. Radioactive Iodine I^{131} in Diagnosis and Treatment of Toxic Goiter. Sidney Werner, M.D. (by invitation), New York, N. Y.
4. Remote Controlled Radium Emanation Plant and Automatic Measuring Apparatus for Gold Implants. John E. Rose, M.D., Chicago, Ill., and Robert W. Swain (both by invitation), Baltimore, Md.
5. Harmful Effects of Irradiation. W. E. Chamberlain, M.D., Philadelphia, Pa.

Tuesday Afternoon, June 7, 1949

Lymphoma Symposium

Lloyd F. Craver, M.D., *Chairman*

1. Interrelationships of Malignant Lymphomas. Philip Custer, M.D. (by invitation), Philadelphia, Pa.
2. Treatment of Myeloma by Urethane. Wayne Rundles, M.D. (by invitation), Durham, N. C.
3. Review of Chemotherapy for Leukopenias and Lymphomas. William Dameshek, M.D. (by invitation), Boston, Mass.
4. Review of Isotope Therapy for Leukemia. E. H. Reinhard, M.D. (by invitation), St. Louis, Mo.
5. Advances in Therapy of Hodgkin's Disease. Frank Bethell, M.D. (by invitation), Ann Arbor, Mich.

SIXTH INTERNATIONAL CONGRESS OF RADIOLOGY

The Sixth International Congress of Radiology will be held in London from July 23 to July 30, 1950. The headquarters of the Congress will be at the Central Hall, Westminster, which will also house an extensive Scientific Exhibit. The Technical Exhibit of apparatus will be located in the Halls of the Royal Horticultural Society nearby.

The Officers of the Congress are as follows:

President—Dr. Ralston Paterson, Manchester.
President-Emeritus—Dr. A. E. Barclay, Oxford.
Vice-Presidents:
Diagnosis—Dr. S. Cochrane Shanks, London.
Therapy—Prof. B. W. Windeyer, London.
Biology—Dr. F. Gordon Spear, Cambridge.
Physics—Prof. W. V. Mayneord, London.
Treasurer—Dr. H. Graham Hodgson, London.
Secretary-General—Dr. J. W. McLaren, London.

The subjects chosen for the main scientific meetings are:

1. General Congress Scientific Meetings.
   (a) "Radiological Achievement, 1937–1950."
   (b) "Mass Radiology of the Chest."
   (c) "Supervoltage Radiotherapy."
   (d) "Radiation Hazards."
2. Diagnosis Section Symposia.
   (a) "Skeletal Changes in Blood Diseases."
   (b) "Radiology of the Small Intestine."
   (c) "Arthrography."
   (d) "Angio-cardiography."
3. Therapy Section Symposia.
   (a) "Method of Presentation of Results of Treatment."
   (b) "Radioactive Isotopes."
   (c) "Cancer of the Larynx."
   (d) "Cancer of the Breast."
4. Biology Section Symposia.
   (a) "Radiation Histology."
   (b) "Radiation Chemistry."
   (c) "Radiation Genetics."
   (d) "Mode of Action of Ionizing Radiations."
5. Physics Section Symposia.
   (a) "Acceleration of Particles and the Generation of Ionizing Radiations."
   (b) "Radiological Units."
   (c) "Radiotherapeutic Physics."
   (d) "Production and Physical Properties of Radioisotopes."

Selected speakers will be invited to contribute the major portion of these symposia. Other sessions will be devoted to the reading of papers proffered by authors on their own topics.

A varied and interesting social programme is being arranged for members of the Congress, and special attention is being paid to the entertainment of Associates accompanying Members.

During the week preceding and the two weeks following the Congress, demonstrations will take place in the radiological departments of a number of London hospitals. Planned tours to centres of interest in Great Britain and Ireland are being arranged to follow the Congress; they will include excursions to the neighbouring countryside by coach, visits to buildings of historical interest, demonstrations at hospitals, and a full social programme.

Those wishing to attend the Congress as Full Members (£7.7s.0d.) or as Junior Members (under thirty years of age on January 1, 1950—£4.4s.0d.) must be members of a radiological society, or sponsored by a radiological society. Ladies and children accompanying Members can be registered as Associate Members (£3.3s.0d.). Associate Membership is also open to technical staff of radiological departments and laboratories, or of the X-ray industry. A late fee will be charged to those registering after April 1, 1950.

Members of the Congress may make their travel and hotel reservations through any office of Messrs. Thomas Cook & Son, Ltd. (or their associated company, the Cie Internationale des Wagon-Lits) who have been appointed the official travel agents for the Congress.

It is planned to issue a detailed Programme with registration forms to the members of radiological societies in April, 1949. All communications in connection with the Congress should be addressed to the Secretary-General at 45 Lincoln's Inn Fields, London, W.C.2.

Note: It has just been learned that H.R.H. The Princess Elizabeth hopes to open the Congress.

BROOKHAVEN NATIONAL LABORATORY NUCLEAR REACTOR

The construction of a nuclear reactor (atomic pile) and auxiliary laboratories is nearing completion at Brookhaven National Laboratory, and initial operation is expected in the fall of 1949. The reactor has been designed to provide a unique facility to serve the needs of the scientific, engineering, and industrial institutions located in the northeastern part of the United States. One of the major design considerations was that the reactor should be able to support an extensive research program. Emphasis has been placed on reliable, safe, and continuous operation.

The reactor is an air-cooled unit constructed of graphite and unenriched uranium. The maximum thermal neutron flux is expected to be about 5×10^{12} neutrons per square centimeter per second. For experiments, one hole 12 inches square, and several 4 inch square holes penetrating the shield at various levels, will permit the insertion of apparatus in the interior of the reactor and the release of collimated neutron beams. The over-all width of the reactor, including the shield, is about 38 feet in the direction of the 4 inch openings. A number of automatic devices will allow controlled irradiation of samples for periods as short as ten seconds. The top shield of the reactor consists of removable 4 foot square blocks. It will accommodate thermal columns and large equipment designed to utilize leakage thermal neutron flux (in excess of 10^{11} neutrons per square centimeter per second). Provision has been made for cages in which large size laboratory animals can be moved under the reactor. It will be possible to conduct research on three vertical faces of the reactor, as well as at the top and bottom.

Laboratories specially designed for handling radioactive materials are included in the reactor building. They will accommodate more than eighty scientists and technicians for research in physics, chemistry, biology, and medicine.

A "hot" laboratory is being constructed near the reactor building; the structure will be linked by a monorail and by pneumatic tubes for transporting irradiated material. Three distinct facilities will be provided in the "hot" laboratory: (1) "hot cells" for remote control processing of samples having up to 50 curies of 2 mev. gamma activity; (2) "semi-hot cells" for handling samples having 1 millicurie to 1 curie of 2 mev. gamma activity, using semiremote control techniques, including tongs and special manipulators; and (3) a "semi-works" area in which large apparatus can be erected with appropriate shielding. The "hot" laboratory building will also include analytical laboratories, shops, store rooms for "hot" and "cold" materials, personnel locker space, and offices. Its completion will be deferred until after the completion of the reactor.

BASIC COURSES IN TECHNIQUES OF USING RADIOISOTOPES AS TRACERS

The Special Training Division of the Oak Ridge Institute of Nuclear Studies announces that three basic courses in the techniques of using radioisotopes as tracers will be held during the summer. In addition tentative plans are being made for two secondary courses in this field.

The basic courses will be similar to a series of seven courses offered at Oak Ridge last summer and during the fall and winter months. Thirty-two participants will be accepted for each of the four-week courses. Each session is divided into laboratory work, lectures on laboratory experiments, general background lectures, and special-topic seminars. In order to give participants a maximum of knowledge and ability in the handling of radioactive isotopes in research, experiments will be conducted covering the use and calibration of instruments, and the purification and separation of radioactive materials from

inert materials and from other radioactive materials. Other laboratory periods will be devoted to the application of various radioisotope techniques. Ample time will be allowed for library work and conferences with the staff on individual problems.

Seminar topics include the use of radioisotopes in animal and human experimentation, principles and practices of health physics, design of radiochemical laboratory, dosimetry, instrumentation, and the effects of radiation on living cells.

The basic courses will be given from June 6 to July 1, July 11 to August 5, and from August 8 to September 2, 1949.

Applications for these courses should be mailed prior to June 1 if possible.

The two secondary courses will be of two weeks' duration and will be open to research workers who have completed the basic course or its equivalent in actual radioisotope work. These courses will be combined symposia and practical sessions in new techniques. One of the two courses, set tentatively for the period September 5–16, 1949, will be devoted primarily to the use of radioisotopes in medical research. Typical work covering the use of sodium, iodine, phosphorus, etc., in medical use will be included in the course. The other course, tentatively scheduled for the period September 19–30, will be concerned primarily with instrumentation. New developments in circuitry, scintillation counters and crystal counters will be taken up in some detail. A competent staff assembled from the field will conduct the secondary courses. Enrollment for the two courses will be limited, and interested individuals should establish contact with the Institute as soon as possible.

A registration fee of $25.00 will be charged for the basic courses. The fee for the secondary courses has not been determined as yet. Dormitory facilities in Oak Ridge, including linen, towels, etc., will be provided at a nominal cost, and food may be obtained in cafeterias and restaurants.

Additional information on the courses and application forms may be obtained from Dr. Ralph T. Overman, Chairman, Special Training Division, Oak Ridge Institute of Nculear Studies, P. O. Box 117, Oak Ridge, Tennessee.

TWENTY-FIFTH ANNIVERSARY OF RADIATION THERAPY DEPARTMENT OF BELLEVUE HOSPITAL

The Twenty-fifth Anniversary of the establishment of the Radiation Therapy Department of Bellevue Hospital under the direction of Dr. Ira I. Kaplan was marked by a special clinical gathering of the Department's Alumni, on March 24, 1949, with lectures by Dr. Bradley L. Coley, "Bone Tumors—A Field Requiring Cooperation Between the Radiologist and the Surgeon"; Dr. Douglas Quick, "Advances in Radiation Therapy in the Past Twenty-Five Years," and Dr. I. C. Rubin, "Twenty-Five Years' Experience with Radiation Treatment for Sterility Associated with Habitually Delayed Periods." Luncheon was followed by clinical demonstration of the work of the department, and the celebration concluded with a Testimonial Dinner to Dr. Kaplan.

DAVID ANDERSON-BERRY PRIZE (1950)

A David Anderson-Berry silver-gilt medal, together with a sum of money amounting to about £100, will be awarded in 1950 by the Royal Society of Edinburgh to the person, who, in the opinion of the Council, has recently produced the best work on the therapeutic effect of roentgen rays on human diseases.

Applications for this prize are invited. They may be based on both published and unpublished work and should be accompanied by copies of relevant papers.

Applications must be in the hands of the General Secretary, Royal Society of Edinburgh, 22 George Street, Edinburgh 2, Scotland, by March 31, 1950.

ABSTRACTS OF ROENTGEN AND RADIUM LITERATURE

Department Editor: George M. Wyatt, M.D., 1835 Eye St., N.W., Washington 6, D. C.

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ROENTGEN DIAGNOSIS

NECK AND CHEST

Olsen, Arthur M. Esophagitis. (Editorial) *Surg., Gynec. & Obst.*, March, 1948, *86*, 372–374.

Apparently esophagitis is a condition which is seldom recognized during a patient's life. Paul has stated that acute ulcerative esophagitis is a common finding at necropsy but rare in clinical practice. Vinson and Butt found that in 75 per cent of their 213 cases of esophagitis (found at necropsy) the patients had been operated upon a short time before. The disease is encountered commonly in patients who have gallbladder disease, duodenal ulcer, obstructing lesions of the gastrointestinal tract and esophageal hiatal hernias. The condition is probably the result of reflux of gastric secretions into the esophagus. The digestive juices are very irritating to the esophageal mucosa. Esophagitis is likely to occur in association with abdominal diseases that produce excessive vomiting.

The cardiac sphincter is incompetent in many cases of esophageal hiatal hernia and esophagitis frequently is associated with hiatal hernia. Many years ago Cushing called attention to the frequent occurrence of esophagitis and esophageal ulceration in patients with lesions of the brain.

The symptoms of esophagitis frequently are overlooked. Such terms as "heartburn" and "sour stomach" are often used to describe a substernal and epigastric burning sensation caused by inflammation of the lower part of the esophagus. In cases in which the disease is severe patients may complain of substernal pain, sometimes referred up to the throat and neck and even into the arms. Such pain usually indicates esophageal spasm.

In most cases esophagitis probably subsides without leaving any ill effects. However, repeated episodes of esophagitis lead to a progressive cicatrization of the lower part of the esophagus.—*Mary Frances Vastine, M.D.*

Gross, Robert E., and Neuhauser, Edward B. D. Compression of the trachea by an anomalous innominate artery; case report. *Am. J. Dis. Child.*, April, 1948, *75*, 570–574.

This report summarizes the authors' experience with the successful surgical treatment of a patient in whom the trachea was compressed by an innominate artery which lay in an unusual position. The patient was an infant girl, aged four months, with symptoms of noisy breathing, particularly during inspiration and a respiratory rate of 44 per minute. There was no cyanosis. Fluoroscopic examination showed no abnormality of the heart or lungs. The swallowing function appeared normal, and no extrinsic pressure was evident in the esophagus filled with barium sulfate. Roentgenograms of the chest showed no abnormality in the anteroposterior position, but in the lateral projection definite narrowing of the trachea could be seen. Iodized oil was instilled into the trachea for better visualization. In the anteroposterior view slight broadening of the trachea just below the

thoracic inlet could be seen. In the lateral view an extrinsic pressure defect was present on the anterior aspect of the trachea. This defect was just above the level of the aortic arch and coursed obliquely upward from left to right. It was thought that this defect was produced by an aberrant artery arising on the left side of the aortic arch and passing obliquely in front of the trachea to its distribution on the right side.

At operation the innominate artery was found to arise from the aortic arch somewhat to the left of its normally expected position, and it had a common origin with the left common carotid artery. As the innominate artery coursed to the right, upward and backward, to reach the thoracic outlet, it forcibly pressed on the right anterolateral and the anterior surfaces of the trachea in such a way as to deform it and reduce the size of the tracheal lumen. The innominate artery was anchored in a forward position by tacking it to the back of the sternum. After operation the baby had an extremely satisfactory convalescence. On the sixth postoperative day, bronchograms showed great improvement in the appearance of the trachea. The slight defect still present did not have the appearance of an indentation due to external compression and it was interpreted as representing a mild structural deformity of the trachea which had developed as a result of the external compression which had existed throughout the life of the baby prior to operation. She was seen three months after operation and was entirely asymptomatic.—*R. S. Bromer, M.D.*

Evans, Titus C. Preparation of radioautographs of thyroid tumors for study at high magnification. *Radiology*, August, 1947, *49*, 206–213.

In an attempt to obtain sharp autoradiographs that could be easily compared with the histologic anatomy of thyroid tumors after administration of radioactive iodine, the author mounted tissue sections directly on the photographic emulsion of a 2 by 2 inch Eastman lantern slide, medium contrast. After photographic processing, these slides were then stained by hematoxylin and eosin and the result gave a complete record of the location of the iodine and the cellular morphology simultaneously. It is felt that this is a definite improvement on the older method of making separate autoradiographs and stained tissue sections and superimposing them for study.—*Robert P. Barden, M.D.*

Quimby, Edith H., and McCune, Donovan J. Uptake of radioactive iodine by the normal and disordered thyroid gland in children. *Radiology*, August, 1947, *49*, 201–205.

Carrier-free radioactive iodine was administered to infants and children to determine its usefulness as an indication of thyroid function. Oral doses of from 20 to 40 microcuries were followed by concentration and retention in the thyroid gland of about 12 per cent in children without thyroid disease, much higher amounts in hyperthyroidism, and less than 1 per cent in hypothyroidism. In the occasional patient without thyroid disease, an extremely low uptake was encountered. The authors feel this may be explained by a high intake of iodine previous to the test, or to debilitating disease at the time of the test.—*Robert P. Barden M.D.*

Hawley, Paul R. The tuberculosis program of the Veterans' Administration. *Am. Rev. Tuberc.*, Jan., 1947, *55*, 1–7.

Responsible for the largest known group of tuberculosis patients, the Veterans Administration may be expected to assume leadership in the fight against this disease. For the peak year of 1950, a need for 15,000 beds is anticipated and this requirement is being met through acquisition of Army hospitals and new construction. The present bed capacity is approximately 6,000.

The ratio of doctors to patients, including various specialists, has been set at approximately 1 to 35, and a goal has been fixed for at least one nurse to five patients.

Through a tuberculosis case-finding program, any veteran who comes to the Veterans Administration will get a chest roentgen examination if he has not had one within the past six months.

Tuberculosis patients will be treated at five types of institution. 1. Tuberculosis units within neuropsychiatric hospitals. 2. Sections of not less than 100 beds in general hospitals. 3. Convalescent rural sanatoriums for ambulant patients. 4. Isolated "health resorts" for patients with positive sputum but for whom definitive treatment is inadvisable. 5. Communities for severely handicapped but ambulant patients with negative sputum.—*J. J. McCort, M.D.*

Russakoff, A. H. Tuberculosis in the Alabama State hospitals. *Am. Rev. Tuberc.*, Jan., 1947, *55*, 93–101.

A mass roentgenographic survey of two state mental hospitals was made using 35 mm. films. Persons found to have suspicious and definite infiltrations were recalled for a conventional 14 by 17 inch film.

Including the known cases of tuberculosis prior to the time of the this study, the overall prevalence of reingestion tuberculosis is 5.0 per cent. Although the results of this study disclose the prevalence of tuberculosis to be lower than that in some other institutions for the mentally ill, the author feels that tuberculosis constituted a major public health problem among patients and employees alike in the Alabama state hospitals.—*J. J. McCort, M.D.*

Hilleboe, Herman E. Recent developments in tuberculosis control. *Am. Rev. Tuberc.*, Jan., 1947, *35*, 17–20.

Within the next five years, the Tuberculosis Control Division will continue its case finding and follow-up program and will set as its goal examination of the majority of persons over fifteen years of age in the population of the United States. Such an intensive campaign will make necessary increased efforts in providing simultaneously medical care and isolation, after-care and rehabilitation and protection of the patient's family against economic distress. Those objectives can be attained in that relatively short period. Then the stage will be set for the final eradication of tuberculosis in the United States.—*J. J. McCort, M.D.*

Woodruff, G. Eugene. The quantitative tuberculin test; its significance in the diagnosis of tuberculosis. *Am. Rev. Tuberc.*, June, 1947, *55*, 488–494.

1. The patient in relatively good general condition who is suspected of having tuberculosis should exhibit a positive tuberculin reaction in confirmation of the diagnosis.

2. In any large series of patients with roentgenograms suggestive of tuberculosis, a certain number will be encountered who fail to react to tuberculin high concentration. The differential diagnosis in such cases is simplified by the knowledge that the patient with active pulmonary tuberculosis who is anergic is always critically ill. Any anergic patient who does not appear ill is probably montuberculous, regardless of the roentgenographic findings.

3. Tubercle bacilli are never found in the sputum of an anergic patient unless he is critically ill.

4. The anergic tuberculous patient is much more likely to have large numbers of tubercle bacilli in his sputum than is the highly allergic patient.

5. Routine tuberculin tests are one of the most important contributions of the laboratory to the diagnosis of tuberculosis.—*J. J. McCort, M.D.*

Baggenstoss, Archie H., Feldman, William H., and Hinshaw, H. Corwin. Streptomycin in miliary tuberculosis: its effect on the pathological lesions of generalized miliary tuberculosis in human beings. *Am. Rev. Tuberc.*, Jan., 1947, *55*, 54–75.

Clinical, roentgenological and pathological observations concerning 5 patients who had fatal miliary tuberculosis treated with streptomycin are reported. Evidence of regression and healing of the miliary tubercles in the lungs was observed roentgenologically in 4 cases, ophthalmoscopically in the choroid layer of the eye in 2 cases and histopathologically in the lungs and liver in 4 cases and in the spleen in 3 cases. The development of widespread tuberculous meningitis apparently was inhibited in 1 case and was either prevented or cured in 2 other cases. No histopathological evidence of any toxic effect of the drug could be found with the possible exception of renal tubular damage which occurred in 1 case. These observations offer further encouraging evidence of the therapeutic efficiency of streptomycin in tuberculosis.—*J. J. McCort, M.D.*

Long, Esmond R. The tuberculosis experience of the United States Army in World War II. *Am. Rev. Tuberc.*, Jan., 1947, *55*, 28–37.

It is known, through sampling done by the Office of the Surgeon General during the war, and through comparison of induction and discharge films of men breaking down, that several thousand small infiltrative lesions were overlooked by the induction station roentgenologists in the millions of films examined. But it is a fair estimate that 90 per cent of the significant lesions that should have been seen were discovered.

Such oversights should never occur in such

number again. The best insurance against their recurrence is a well-trained, stable personnel, experienced in the detection of tuberculosis, and on duty in sufficient numbers so that no man is expected to carry a load of more than 300 films a day over prolonged periods of time. From the point of view of administrative efficiency, the author believes this personnel should be military, not civilian. It would be preferable to hold young officers in Army training stations longer and then keep them on the job. Substitution of tuberculosis experts trained in reading chest films only, as from time to time suggested, would not solve the problem. Chest lesions of incredible variety are seen in induction stations and one-fifth of the films taken are of other parts than the chest.

The Army does not consider the long range care of tuberculosis a proper responsibility of the Army Medical Corps. Tuberculosis requires long treatment, and, as far as possible, that care should not be broken up. It should proceed in an orderly manner in one sanatorium, with proper convalescent follow-up and modern rehabilitation measures. The system of Veterans hospitals has been set up for this purpose.—*J. J. McCort, M.D.*

Siltzbach, Louis E. Carcinoma simulating pulmonary tuberculosis. *Am. Rev. Tuberc.*, Feb., 1947, *55*, 170–176.

The author reports on 2 cases which were treated for pulmonary tuberculosis for periods of seven and sixteen months, respectively, before the neoplastic nature of the lesions was recognized. A proper evaluation of the alterations in the appearance of the lesion on successive films was crucial in both these cases, since neither of the patients had any symptoms for the many months of observation prior to surgery.

The progression of the lesions on the roentgen film in these 2 cases may be summed up as follows: Initially, both lesions measured about 2 cm. and had a veil-like, somewhat amorphous appearance, but on close inspection it could be seen that the mesial borders were rounded where as the lateral borders faded out and were streaky. These streaked shadows probably represented small foci of atelectasis arising either from obliteration of small bronchial lumina by the neoplasm or from pressure exerted upon the lumen by the expanding extramural mass.

Later, the shadow became denser and more sharply demarcated from the surrounding lung parenchyma and it then represented the neoplasm itself. A distinguishing roentgen feature in the second case was central necrosis of the neoplasm, which was suggested by the presence of several small irregular areas of lesser density within the solid shadow. The author states that should such areas be visible within the mass on the initial film and should the sputum be persistently free of tubercle bacilli, such a lesion must be preserved to be neoplastic and exploratory operation is warranted.—*J. J. McCort, M.D.*

Rigler, Leo G., and Kelby, Gjert M. Emphysema; an early roentgen sign of bronchogenic carcinoma. *Radiology*, November, 1947, *49*, 578–586.

The authors report 5 cases in detail and mention 2 additional cases in which obstructive emphysema was an early manifestation of bronchogenic carcinoma. According to Westermark the effects of bronchostenosis may be divided into the following four stages: 1. Diminution of aeration as the result of minimal stenosis. Cases in this stage are difficult to detect roentgenologically. 2. The stenosis becomes of higher grade. Air can enter during inspiration but due to diminution in the size of the bronchial lumen during expiration it is much more difficult for it to escape. This results in relative emphysema of the abnormal lung, which may not be evident in a roentgenogram made in inspiration but which can be readily detected under the fluoroscope or in a film made in expiration. 3. As the stenosis increases there will come a stage when there is inspiratory as well as expiratory emphysema. 4. When the tumor with its debris or inflammatory products completely occludes the bronchus, atelectasis results.

As the only hope of curing bronchogenic carcinoma is early diagnosis, careful study should be given to minor differences in radiability of the two lungs to determine whether obstructive emphysema is present. Such a finding should lead to further investigation by bronchography, planigraphy, and bronchoscopy. Patients suspected of bronchogenic carcinoma but without frank roentgen findings should always be examined in expiration as well as inspiration.—*Arthur E. Childe, M.D.*

Valle, Anibal Roberto, and White, M. Lawrence, Jr. Pulmonary tuberculosis simulating bronchogenic carcinoma; report of four cases. *Am. Rev. Tuberc.*, May, 1947, *55*, 449–456.

In spite of modern methods, differential diagnosis is often difficult in these cases without exploration. In this series, cough, gradually becoming productive, small hemoptysis, chest pain, weight loss, and weakness were all symptoms common to bronchogenic carcinoma and tuberculosis or other chronic inflammatory disease. In 3 cases of this series orthodox methods, carefully and repeatedly applied, failed to reveal tuberculosis, in spite of active lesions, both clinically and pathologically. In the fourth case pathological inactivity of the lesion makes the negative studies less surprising. The roentgen picture in all cases was suggestive of carcinoma and the bronchoscopic examinations were noncontributory.

The authors summarize by stating that diagnostic mistakes revealed only at or after operation must be accepted if we are to make an effective attack on cancer of the lung. They can be excused only if conscientious and complete attempts at ruling out tuberculosis have been carried out.—*J. J. McCort, M. D.*

Birath, Gösta. Pulmonary function following pneumothorax. *Am. Rev. Tuberc.*, April, 1947, *55*, 349–365.

Twenty-five patients with pleurisy with effusion without parenchymal lesions, and in whom so-called preventive pneumothorax treatment had been terminated, were examined by the author's method for the estimation of the total lung volume and its subdivisions and of the respiratory dead space.

The following results were obtained:

1. Total and vital capacities were diminished.

2. Equilibrium and residual capacities were not generally diminished to the same degree.

3. While the diminished total and vital capacities were due to the impairment of the thoracic and diaphragmatic mobility through pleural adhesions the cause of the increased relative lung volume values was a hypoventilation of certain parts of the lung, provoked by the same cause. In 11 cases of terminated pneumothorax treatment chosen to throw light on the subject, and with more or less extensive parenchymal lesions, the following was found.

4. The lung function, in several cases, was seriously impaired, manifesting itself in low total and vital capacities, considerable increase of the relative lung-volume values and in certain cases increased values for the respiratory dead space.

5. The cause of this was, in some cases, in part parenchymal contraction with so-called compensatory emphysema and reduction of the parenchyma, but in the majority of cases the cause was pleural changes following pneumothorax treatment (venilatory insufficiency).

6. In view of the very serious impairment of function that may result when a lung retraction complicates pneumothorax treatment, it is suggested that in certain cases this treatment should be abandoned and replaced with other collapse measures.—*J. J. McCort, M.D.*

Ingegno, Alfred P., D'Albora, John B., Edson, John N., and Gianquinto, Peter J. Pneumonia associated with acute salmonellosis. *Arch. Int. Med.*, April, 1948, *81*, 476–484.

In an outbreak of acute salmonellosis, due to *Salmonella montevideo*, 19 patients had evidence of bronchopulmonary involvement. Four had acute bronchitis. One patient had definite bronchopneumonia with sputum which contained the *Salmonella* organism. The other 14 patients had interstitial pneumonia. The pathogenesis of the interstitial type is unknown, but the clinical and roentgenologic features suggest a virus origin.

Roentgenologic examinations of the chest show changes interpreted as indicative of interstitial pneumonia in all patients. In 8 the changes were bilateral, while in 6 the right side only was affected. These interstitial changes were patchy or diffuse and in 2 instances were accompanied with partial consolidation. In 1 patient there was evidence of pleuritis at the base of the right lung. Resolution began within four to seven days of onset and in almost all was completed in about two weeks. There was neither clinical nor roentgenologic evidence of any suppuraative complication.

A scattering of other symptoms and signs include asthenia, general malaise, anorexia, herpes labialis, chills, aches and pains, neuritic pains and dysesthesias, sweats and transient urticaria.

It may be assumed that true *Salmonella* bronchopneumonia with pulmonary consolida-

tion is probably a relatively rare manifestation of salmonellosis. Diagnosis is established by demonstration of the causative organism in the sputum or puncture of the lung.—*Eugene J. McDonald, M.D.*

Adams, John M. Congenital pneumonitis in newborn infants. *Am. J. Dis. Child.*, April, 1948, *75*, 544–554.

A relation between infections of the upper respiratory tract in mothers and primary pneumonitis in their infants is considered likely by the author. He suggests that the same causative factor may be involved and that this agent may be responsible for pathologic changes in the pharyngeal epithelial cells of both the mother and her baby. These changes are represented by large numbers of typical cytoplasmic inclusion bodies seen in the pharyngeal epithelium of both mother and the baby and in the alveolar and bronchial epithelium of the infants who die of pneumonitis.

Reports of 6 cases of congenital infections of the respiratory tract are given, together with a brief review of the pertinent features of primary virus pneumonitis with therapeutic suggestions. Roentgenograms of the chest in several of the cases showed slight infiltration, a soft diffuse shadow in the lungs, in the right upper and lower lobes and in others there was a distinct increase in the bronchovascular markings in both lungs. The disease in the newborn and young infants is characterized clinically by an acute onset of sneezing, coughing, dyspnea and cyanosis. The elevation in temperature was moderate to low, some infants showing no elevation. The mortality was definitely correlated with the severity of symptoms and signs.—*R. S. Bromer, M.D.*

Lemone, David V., Scott, Wendell G., Moore, Sherwood, and Koven, A. Link. Bagasse disease of the lungs. *Radiology*, November, 1947, *49*, 556–567.

Bagasse is the name given to sugar cane after it has been crushed and the juice extracted. Bagasse disease of the lungs, or bagassosis, is a pulmonary disorder brought about by the inhalation of dried bagasse dust.

Bagasse fibers are tough and possess insulating qualities. Bagasse is being used more extensively in the manufacture of thermal and noise-insulating building materials and in the manufacture of refractory brick. Unless properly handled, it constitutes a serious industrial hazard. About 40 cases of bagassosis have been reported in workers in sugar cane processing plants, and in plants where the bagasse is manufactured into building boards or refractory brick.

The symptoms and clinical course of bagassosis are variable, depending on the length of exposure and the density of the inhaled dust. In general, about two months of exposure to the dust are required before symptoms appear. Onset is insidious, the patient usually not realizing that he is ill until he is seized by a sudden coughing spell and extreme dyspnea. An acute febrile illness follows, or acute bronchiolitis. In lighter cases of briefer exposure, the disease clears up in two to six months. Patients with long exposure are critically ill. An 8.3 per cent mortality rate has been reported in one series.

Eosinophilia is usually present. Roentgenographically, a diffuse fine punctate infiltration is seen, which tends towards a nodular appearance as the disease starts to clear up. Areas of consolidation may be present, especially in and near the hilum. The roentgen findings are not diagnostic, but the reversibility of the process distinguishes it from the other pneumoconioses.

The exact etiology of the disease is obscure and there is no specific treatment. No response to chemotherapy has been observed. Oxygen affords some relief from the dyspnea in the more severe cases. The authors report 3 cases in detail.—*George Cooper, Jr., M.D.*

GENERAL

Pautrier, L. M. Sarcoidosis. *Brit. J. Tuberc.*, January, 1948, *42*, 1–7.

The author discusses two prevalent theories of the etiology of sarcoidosis: namely, the concept of a tuberculous origin and the belief of an indeterminate virus as a cause. To refute the first the author points out that the histopathological picture of sarcoid is not characteristic of tuberculosis; no tubercle bacilli are found in lesions of sarcoid; and the tuberculin test is usually negative. He dismisses the belief that sarcoid is genuine tuberculosis modified by special reactions on the part of the organism. He analyzes the evidence with respect to the second theory and finds little support for it. The reliability of the Kveim reaction, which has been advanced as proof for such a belief, has been questioned by some investigators.

The writer feels that sarcoidosis is clinically an autonomous disease and not a single monomorphic tissue reaction produced by various agents. He concludes that the etiology remains unsettled.—*Harry L. Berman, M.D.*

HAXTHAUSEN, H. On the Kveim reaction in Boeck's disease. *Brit. J. Tuberc.*, January, 1948, *42*, 7–11.

The author discusses the role of the Kveim reaction in attempting to decide whether sarcoid is a form of tuberculosis or a disease per se. The Kveim test consists of the intradermal injection of a suspension of granulation tissue characteristic of the disease. The reaction appears after a latent period of one to two weeks or longer and consists of a papule increasing in size to a small nodule and disappearing in several months to two years. The test has been considered to be positive "nearly always" in sarcoid and negative in other diseases. The pathogenesis of the reaction is not entirely clear. Some features suggest an isomorphic reaction; that is, the local reproduction in the skin of a lesion found elsewhere in the body. Other features suggest a specific allergic reaction. The author emphasizes the need for further study and concludes that the Kveim reaction has not settled the controversial aspects of the nature of sarcoid.—*Harry L. Berman, M.D.*

FREUDENTHAL, W. Sarcoid. *Brit. J. Tuberc.*, January, 1948, *42*, 11–16.

In analyzing the chief features of sarcoid which are considered to be proof against the tuberculous etiology of the disease—namely, the histopathological picture, the negative tuberculin reaction, and the absence of tubercle bacilli in the lesions—the author presents evidence showing that these arguments are not entirely correct. He demonstrates typical Langhans' giant cells in some cases of sarcoid, distinct inflammatory components in others, and sarcoid-like pictures in cases of lupus muliaris facei. He calls attention to the fact that positive tuberculin tests are changed to negative during the course of certain infectious diseases and are modified by prior injections of BCG vaccine and tuberculin. As regards the presence of tubercle bacilli, it is claimed that positive cultures are being obtained. Furthermore, the bacilli are seldom found in lesions of the tuberculous dermatoses. The author states that the problem of the nature of sarcoid is still unsolved but that the findings described above are compatible with a tuberculous etiology.—*Harry L. Berman, M.D.*

REFVEM, OLAV. I. Chronic granulomas in the alimentary tract caused by minute mineral particles. II. "Boeck's disease" and occurrence of minute mineral particles. *Acta path. et microbiol. Scandinav.*, January–February, 1948, *25*, 107–121.

A series of conditions in the alimentary tract, such as gastric or intestinal cellulitis, regional enteritis, anal abscess or anal fistula, have been regarded as foreign body reactions, isolated or combined with a bacterial infection. The presumptive foreign body etiology in these cases is supported by few observations and mainly by theoretical deductions. For this study the polarization microscope was used systematically in a series of cases. It was used chiefly to detect cholesterol crystals. Frequently oil droplets, mucous material, hairs, talcum particles were found. In animal experiments silica was injected and often produced a picture resembling the histopathological manifestation of tuberculosis.

Where the foreign bodies are few and very small, the differentiation from smudge may be very difficult. To be accepted as a causative agent, the particles must be situated exactly in the same plane as that of the tissue and naturally embedded in the pathological tissue. The main problem to decide, when foreign material is found, is whether its presence can explain the whole or part of the clinical picture. Foreign bodies were found in about 25 per cent of 209 cases examined. In the anorectal region 34 per cent showed foreign bodies and 75 per cent of these cases showed talc foreign bodies. About two-thirds of talc fistulas in the anal region occurred in men.

II. Histological sections from 100 cases diagnosed as Boeck's disease were examined in polarized light, each case represented by biopsy from one or several lesions. Most of the various sections when examined by polarized light almost always showed a foreign body granuloma embedded in giant cells. The author stresses the possibility of foreign bodies being one of the causes of Boeck's disease. He believes the remissions may be due to a breakdown and disappearence of certain foreign bodies in the tissues.—*Robert J. Reeves, M.D.*

Bjørnstad, Roar Th. Progressive Boeck's sarcoid associated with protracted destructive tuberculosis. *Acta tuberc. Scandinav.*, 1948, *22*, 143–153.

The coincidence of Boeck's sarcoid and tuberculosis is a rather infrequent occurrence, considering the high incidence of tuberculosis alone. Every eighth individual in Norway dies of tuberculosis. One case is reported showing no regression of the sarcoid manifestations in spite of the patient having a protracted, destructive tuberculosis. The tuberculous and sarcoid manifestations did not seem to have any mutual influence upon each other. Reports are given of cases showing regression of sarcoid lesions in connection with the development of a tuberculous process. On studying different papers by the author, one is not convinced that there is a spontaneous regression of sarcoid as the tuberculosis develops but that this may be more of a coincidence.—*Robert J. Reeves, M.D.*

Mueller, J., and Pedrazzini, A. Morbus Besnier-Boeck mit Übergang in Miliartuberkulose. (Besnier-Boeck disease with transition into miliary tuberculosis.) *Schweiz. med. Wchnschr.*, February, 1948, *78*, 126–128.

This is a case report of a twenty-seven year old patient in whom the diagnosis of Boeck's disease was made in 1937 on the basis of hilar lymphadenopathy. His general condition remained good and the local pathology stationary for ten years. Tuberculin reactions were essentially negative during the same period. His terminal illness started with spiking elevations of temperature, acute and profound malaise, rapidly leading to his death. A roentgenogram of his chest revealed miliary dissemination. Also the tuberculin reaction had now become positive in a dilution of 1:100,000. Postmortem examination revealed miliary tuberculosis and hyalin-nodular changes of the paratracheal and paraesophageal lymph nodes as seen in Boeck's disease.—*A. Grishman, M.D.*

Gardner, Clarence E. Foreign body localization in the soft parts; a simple method requiring no especial training or equipment. *Surgery*, February, 1948, *23*, 275–277.

The author reports that Reed and Black, in a review of the literature in 1938, classified the methods of localization of foreign bodies under ten different principles. The method used in 110 cases was reported. It consists of the insertion, under roentgenoscopic control, of two long slender needles. They are inserted at right angles into the tissue at a distance from the proposed incision so that they cross in the approximate location of the foreign body. Anteroposterior and lateral views then are exposed and, with the needle still in place, the field is draped and the area explored at operation.—*Frank H. Marek, M.D.*

ROENTGEN AND RADIUM THERAPY

Loebell, M. A. Simultaneous cross-radiation. *Radiology*, June, 1947, *48*, 570–578.

In February, 1938, in a paper written by the author the advantages of simultaneous cross radiation were discussed and a description was given of apparatus built for that specific purpose. The original model was improved, the present apparatus consisting of a shock proof, oil-filled, lead-lined steel tank containing a 200 kv. transformer surrounded by 4 balanced roentgen-ray tubes. Changing the position of the openings in the regulating diaphragm makes possible the dovetailing of roentgen-ray beams which may be concentrated on a tumor with little cross radiation outside of the neoplasm. Targets are arranged at 60° angles. A series of heavy lead diaphragms, encased in sheet steel, each of which has four apertures, is calculated to allow the roentgen-ray beams to cross at different depth levels of 1 cm. variations below the surface of the skin. The relative position of the openings in the diaphragms determines the level of cross radiation. On each diaphragm is indicated the thickness and kind of filter and the exact target-skin distance. Because of the variation in the size of roentgen-ray beams at different levels apertures in the several diaphragms differ slightly in size, so that the area of cross radiation in the present model is exactly 100 sq. cm. at all levels.

Theoretically, the ideal method of irradiating a tumor would be to give a saturation dose and then repeated smaller doses at frequent intervals, keeping the saturation point constant during the entire cycle of malignant cell mitosis. In deep-seated tumors the danger to adjacent healthy tissues constitutes an obstacle. This difficulty is solved in part by changing the position of the patient, or the course of entry, or both, in such a manner that the roentgen-ray beams cross their own path at a certain depth

below the skin, producing a radiation effect of greater intensity at the tumor depth, and distributing the superficial dose over a larger area. Simultaneous cross radiation is based on the principle of administering quickly large doses of radation at depth and distributing the superficial dose over large areas through a great number of ports at the same time. The advantage lies in the fact that a carcinocidal dose can be administered to a neoplasm, while the tumor bed, receiving a non-lethal dose, recovers quickly and is capable of replacing destroyed malignant structures with benign fibrous tissue, blood vessels and the like. Large daily doses applied directly to a neoplasm tend to keep the saturation point constant and the result compares favorably with that obtained in superficial therapy. A carcinocidal dose can be administered with simultaneous radiation at any depth. This is made possible by the great number of ports of entry (32 or more) through which roentgen-ray beams are brought to converge on any specific area, producing a homogeneous radiation effect.

Eleven case reports are given. In a boy of three years an osteolytic tumor involving the right sacroiliac junction was shown on biopsy to be due to a sarcoma. The boy was treated by the multiple port method for a total tumor dose of 2,146 roentgens. Six years later the child appeared well without any sign of recurrence.—*Samuel G. Henderson, M.D.*

Craver, Lloyd F. Lymphomas and leukemias. *J.A.M.A.*, Jan. 24, 1948, *136*, 244–248.

In spite of the fact that it is doubtful if anyone is in a position to authenticate a claim to have cured any case of Hodgkin's disease, lymphosarcoma, mycosis fungoides or leukemia up to the present time, early diagnosis and treatment of these diseases affords better results in terms of long control. Hodgkin's disease and lymphosarcoma of unicentric origin offers the possibility of cure or eradication by complete surgical excision, heavy regional irradiation, or a combination of both when the disease is confined to one organ or nodal mass. Lymphosarcoma in certain regions such as the head and neck may show a postoperative survival which is double the rate for lymphosarcoma of all types. Surgical survivals seem to exceed irradiation survivals of those with localized lesions, although the groups are not clinically comparable.

For chronic leukemia, a great deal can be accomplished in a palliative way by judicious irradiation even though one must accept incurability as the first premise. Early diagnosis cannot wait for the development of typical textbook symptoms and signs. Early biopsies of Hodgkin's disease and lymphosarcoma frequently fail to reveal the diagnosis and early blood counts may not reveal leukemia.

It is urged that enlarged lymph nodes be investigated for cause and biopsied if no primary lesion is found. Biopsy of more than one node is often advisable. Unicentric lymphomas may be disguised as solitary nodules in the thyroid, breast, base of the neck between the sternocleidomastoid muscle insertions, tonsil, mediastinum, skin, orbit and lacrimal gland, and as a reticulum cell sarocma of bone. Chronic lymphatic leukemia may produce as its first manifestation local tumors reported on biopsy as lymphosarcoma. The use of sternal puncture to detect early lymphatic and myeloid leukemias is important. Osteosclerotic anemias mimic myeloid leukemia by producing compensatory splenic enlargement.

Prevention of these diseases may be gained in some measure by control of exposure to benzene solvents, radioactive emanations, sulfonamide drugs in children, chronic infections, atypical variants for tuberculosis, allergies, heredity, and endocrine dyscrasias. No attempt is made to formulate any set of rules for prevention of these diseases.

Treatment of lymphomas and leukemia by nitrogen mustard, radioactive isotopes, and urethane affords only palliative results. It is clear that these toxic constitutional agents have little or no place in the treatment of early localized Hodgkin's disease or lymphosarcoma. For such cases adequate local roentgen therapy remains the treatment of choice, except perhaps in those cases that lend themselves to radical surgical procedures, which should probably be followed by moderately heavy local postoperative roentgen therapy. Adequate roentgen-ray dosage should be far more than just enough to cause regression. Fractional dosage to skin tolerance is recommended for local areas. Total body irradiation following local irradiation will unpredictably confer longer freedom from relapse in Hodgkin's disease and lymphosarcoma. Doses of 75 to 125 r, in air, are used. Myeloid leukemia responds best to splenic irradiation in daily fractions. Lymphatic leuke-

mia with splenohepatomegaly, enlarged peripheral nodes and bone marrow changes may derive benefit from 200 r to 300 r once around each of the external lymph node bearing areas. It is recalled that some cases of lymphatic leukemia show no enlarged lymph nodes, and some myeloid leukemias do not have splenic enlargement.—*J. A. Campbell, M.D.*

Walker, H. John, and Schulz, Milford D. Carcinoma of the tonsil; a review and its results in a group of ninety cases. *Radiology*, August, 1947, *49*, 162–168.

This is a study of 90 cases of carcinoma of the tonsil seen at the Collis P. Huntington Memorial Hospital from 1936 through 1941, and Massachusetts General Hospital from 1936 through 1945.

Histopathologically this group of tonsillar carcinomas were, in the majority of instances, of a high grade of malignancy, and approximately 90 per cent of them were squamous cell in type. The remaining 10 per cent consisted of lymphoepitheliomas, transitional cell carcinomas, and sarcomas.

It is of importance that 60 per cent of these cases presented themselves with cervical metastases when first seen and that in two-thirds of this group the "lump in the neck" was the first subjective complaint of the paitent.

Methods and types of radiation treatment used varied with the individual case. The authors stress the necessity of varying the treatment to the needs of the individual cases rather than stereotyped plan of treatment for all cases. Fifty patients were treated with supervoltage (1,000 kv. at the Huntington Hospital, and 1,200 kv. at the Massachusetts General Hospital) and 45 patients were treated with 200 kv. Total dose in the series treated with supervoltage varied from 2,400 to 6,600 r, measured in air, through a single lateral portal, the optimum dose being considered 6,000 r, the total dose with high voltage being 3,000 to 4,000 r to each of two opposing portals, measured in air. Some cases were given additional treatment, 2,500 to 3,000 r, through an intraoral cone. A few cases were also treated with interstitial radium in conjunction with roentgen roentgen therapy, both to primary tumor and metastatic cervical nodes. Neck dissection was not employed in any of the 90 cases.

The five year survival group in the entire series was 15 per cent. This survival rate compares favorably with other large series published in recent years. The authors, in comparing their results with other published studies on carcinoma of the tonsil where various forms of therapy have been used, telecurietherapy, interstitial irradiation, neck dissection, electrocautery, postulate the query as to whether any single procedure, or even several procedures can offer increased life expectancy to the patient with malignant tonsillar tumor beyond that afforded by roentgen irradiation alone. The authors do not make any definite statement as to apparent improved survival rate in those patients treated with irradiation produced with supervoltage equipment.—*E. A. Addington, M.D.*

Windholz, Frank. The biological significance of fibrinous radiomucositis of the larynx. *Radiology*, February, 1947, *48*, 157–160.

The author comments that previous writers have pointed out that the appearance of an extensive and confluent radiomucositis indicates that the dose necessary to destroy tumor cells has been reached. In the author's experience both clinically and by study of microscopic sections, he has found that delay or absence of radiomucositis with standard dosage techniques does not necessarily mean that the cancer is not radiosensitive. He states that it merely signifies the inability or diminished ability of the connective tissue to produce fibrin. He also states that the early appearance of irradiation mucositis holds promise that a cure will be obtained. The author also stresses the interrelationship of the appearance of radiomucositis with the reactions of the connective tissue to radiant energy. He concludes, therefore, that radiomucositis is indicative of the degree and extent of connective tissue reaction and that the more marked and earlier the connective tissue reaction is, the more chances for the success of radiation therapy.—*Moris Horwitz, M.D.*

Windholz, Frank. Reactions of connective tissues after protracted fractionated irradiation of laryngeal carcinoma. *Radiology*, February, 1947, *48*, 148–156.

While much attention has been given in the past to the radiopathology of the mucosa following protracted fractionated irradiation of laryngeal carcinoma, little has been written concerning the changes occurring in the con-

nective tissues following such irradiation. The author has beautifully demonstrated the changes appearing clinically and microscopically in the connective tissue following various doses of protracted and fractionated radiation. The author shows that the changes in the connective tissue are marked and extensive and appear both early and late in the course of the radiation administered. He also stresses the fact that when such radiation is given without fractionation the connective tissue changes which are seen to occur are irreversible and much more advanced. After protracted fractionated irradiation there are definite reversible changes noted with healing of the affected areas. These changes have also been demonstrated by the author in animal experiments.

The author divided the reactions occurring in the connective tissue following protracted fractionated irradiation into three periods: The first is a bionegative, retrogressive period characterized by exudation of fibrin, loss of nuclear staining, and frequent changes in the microchemical reaction of subepithelial collagenous fibers. This period appears coincidental with the fibrinous radiomucositis and disintegration of the epithelial cells of the mucous membrane. The author refers to the second period as that of the "biopositive regenerated period." In this period the connective tissue appears to fill out the spaces remaining after disintegration of the tumor. The fibrinoid necrotic collagen of the lamina propria is replaced by hyaline sclerotic layers. The author states that myogenous giant cells indicate the regenerative tendencies of these tissues. The inflammatory reaction of the newly regenerated connective tissue is markedly reduced and is said to be a specific effect of radiation on this structure. This has been shown by animal experiments, as well as in human tissue. The endothelium of damaged blood vessels during this period discloses obliterative changes with connective tissue proliferation. The author refers to the third period as "retrogressive" period, and this is said to occur in those cases which have been improperly irradiated or in which there has been marked sensitivity of the individual connective tissue. In these cases the newly formed connective tissues become necrotic and the mucous membrane discloses ulcerations with secondary infection which infiltrate the deeper layers of the irradiated larynx.—*Moris Horwitz, M.D.*

Hale, Clayton H., and Holmes, George W. Carcinoma of the skin; influence of dosage on the success of treatment. *Radiology*, June, 1947, *48*, 563–569.

Results were compared in the treatment of approximately 1,500 carcinomas of the skin on 1,300 consecutive patients (excluding lesions of the mucocutaneous junction) treated at the Massachusetts General Hospital during the period 1930–1944, with a view toward establishing the relation of particular dosages to success or failure of treatment and determining therefrom an optimal radiation dose.

Three hundred and eighty-seven lesions were treated surgically and 1,035 by roentgen irradiation. All the cases were followed from one to five or more years. The dosages varied from 1,200 to 6,000 r, measured in air. In 89 per cent of the irradiated cases, treatment was given in a single dose while in the remainder of the cases it was fractionated over a period of one to three weeks. Results are plotted in percentage of failures against average total dosages for single massive and fractionated treatments and the expectancies of tumor control in the various dosage ranges employed, are tabulated and discussed.

The studies indicated that 3,200 r to 3,600 r would be required by fractionation over one week to produce the same results as obtained by 1,900 r to 2,200 r by the massive single dose method.

The dose 4,500 r delivered in multiple treatments within one week, or its biological equivalent of 2,700 r by the single dose method, was suggested as an optimal dose to be delivered to a carcinoma of the skin.

Tables and discussions correlate the percentages of failures with the (1) various dosage ranges for the one week fractionation method, (2) different physical modalities for the single massive and fractionated techniques, (3) surgical as against roentgen treatment, (4) sizes of the lesions and (5) time interval between treatment and breakdown.—*E. D. Hudack, M.D.*

Pohle, Ernst A., and Morton, James A. Roentgen therapy in arthritis, bursitis, and allied conditions. *Radiology*, July, 1947, *49*, 19–25.

Roentgen therapy has been used for years in arthritis. One hundred heterogeneous cases were treated and 92 followed. Treatment was given with 400 kv. and 200 kv. Three doses of

150 r or 200 r were given. Forty per cent had two series. Seventy-five per cent of the patients reported moderate to complete relief. Placebos were not used. Harmful effects did occur occasionally. In bursitis 84 per cent received complete or satisfactory relief. Acute cases stand best chance of relief. Conclusion is made that the value is in analgesic effect.—*E. C. Baker, M.D.*

MacCarty, William C. Effects of estrogenic therapy on osseous metastases from carcinoma of the prostate. *Radiology*, July, 1947, *49*, 54–61.

The author reports on the estrogenic treatment of 29 patients showing osseous metastases from carcinoma of the prostate gland. Six were treated by orchiectomy alone, 21 by orchiectomy and stilbestrol, and 2 by stilbestrol alone.

In 10 cases the osseous metastases were thought to be favorably influenced, and in 5 of these there was definite improvement.

The metastases completely disappeared in 2 instances. In 1 of these cases there was complete recalcification of the metastatic area nineteen months after orchiectomy as the sole treatment. The second patient had had carcinoma of the prostrate gland for eight years. Roentgen therapy to the pelvis had been given with temporary improvement. Recurring metastatic lesions in the lumbar vertebrae completely disappeared eighteen months after orchiectomy and subsequent stilbestrol therapy; there had been no recurrence thirty-four months after orchiectomy, eleven years after the original diagnosis.

In 5 cases the osseous metastases became more dense and discrete. In 1 instance the metastases disappeared, only to recur with extensive osteoblastic metastases of a different type from those originally seen.

The author makes the point that the radiologist must be familiar with alterations in bone lesions produced by estrogenic therapy.—*Arthur A. Brewer, M.D.*

MISCELLANEOUS

Gianturco, Cesare. Elastic ruler for roentgen pelvimetry. *Radiology*, July, 1947, *49*, 95–96.

The author describes a correction measuring device consisting essentially of a rubber band upon which a centimeter scale has been marked. Stretching of the band produces distortion of the scale. Scales of known distortion permit determination of the degree of stretching of the band necessary to provide the proper correction for various levels in the bony pelvis. Subsequent films must be made at the same tube-film distance as used in making the distorted scales. The author claims the measurements are "quite as accurate" as those obtained by other methods.—*Chauncey N. Borman, M.D.*

Lipp, Charles S., and Smith, Rector. Latex cap for radon ointment treatment. *Radiology*, February, 1947, *48*, 161–163.

The authors describe the need for, and the preparation of a latex cap for radon ointment treatment. The method described is fairly simple and has wide application, especially in areas requiring the application of radon about the head and neck and in other small surface areas of the body. An advantage also mentioned is the fact that the latex cap may be used over and over again after being cleaned and sterilized.—*Moris Horwitz, M.D.*

Vincent, James G., Vincent, Helen Whitgrove, and Dowdy, Andrew H. Experimental clostridial infections in dogs. *Radiology*, June, 1947, *48*, 610–627.

The authors experimented with prophylactic and therapeutic measures on experimentally induced clostridial infections in dogs. The experiments included both pure strain organisms and mixtures of the various clostridia and *Staphylococcus aureus haemolyticus*. The prophylactic and therapeutic agents used were as follows: (1) roentgen ray, (2) oxygen gas, (3) oxygen gas and roentgen ray, (4) sulfadiazine, (5) sulfanilamide, (6) butyryl sulfanilamide, (7) sulfathiazole, (8) penicillin, (9) pentavalent antitoxin, (10) toxoid. Prophylactically sulfadiazine was found the most effective sulfanamid employed, although it was valueless against *Cl. oedematiens*. Therapeutically sulfadiazine was far from routinely effective. Early penicillin therapy in massive doses gave better results. When administered in small doses or late in the development of the disease this agent was not very effective.

Polyvalent antitoxin in massive doses administered rapidly was useful as late as twelve hours after inoculation. Smaller doses over a longer period of administration were relatively ineffective. Combined penicillin and antitoxin therapy gave the best results. In order to

minimize residual cardiac damage, early and adequate antitoxin therapy appears indicated.

Cl. welchii toxoid immunization protected dogs against a pure strain of *Cl. welchii*.

In the discussion Dr. Robert P. Barden emphasized the importance of the initial cleansing of the wound, the immediate bandaging and the sanitary care which the wound received. In human battle casualties the sulfa drugs, penicillin, antitoxin and early surgery are all important therapeutically. Dr. Barden is convinced that roentgen therapy is of no value. Dr. James F. Kelly took exactly the opposite stand and illustrated his point with clinical material. Dr. Dowdy, in closing, indicated that roentgen therapy is of some value but is not to be preferred over antitoxin and penicillin. In the future active human immunization will probably be possible.—*Oliver P. Winslow, Jr., M.D.*

Raper, John R. Effects of total surface beta irradiation. *Radiology*, September, 1947, *49*, 314–324.

This research was carried out at Clinton Laboratories, Oak Ridge, Tennessee, under the Manhattan Project. In order to study the effect of energy absorption distribution on biological effect, laboratory animals including mice, rats, guinea pigs, rabbits, and one-day-old baby rats were exposed in sufficient numbers to establish the pattern effects in each species. The animals were placed in plastic boxes lined with panels of phosphorus^{32} bakelite so that the animal received an equal dosage of beta rays over its entire surface. Gross effects, and the time of their appearance after irradiation, were noted. Effects such as inflammation of the eyes, eyes watery and/or sealed shut, epilation around the eyes and snout, erythema on feet and ears, hyperemia and subsequent drying of the ear tips, severe epilation, local desquamation, and ulceration were noted in relation to the time of exposure. The effects of beta irradiation varied with each species so that an acute lethal action occurred at a characteristic dosage. The main wave of mortality occurs at a somewhat later postirradiation time than following irradiation with roentgen rays or gamma rays and for lethal studies with beta rays forty-five days has been arbitrarily chosen to define a survivor in contrast to twenty-one days' survival commonly used for roentgen rays and gamma rays. The lethal action of beta rays must necessarily be brought about differently than that induced by penetrating radiations since all the energy of beta rays is absorbed in a superficial layer of tissue whose mass is small relative to the total mass of the animal. It follows then that the total energy absorbed to produce 50 per cent killing is directly proportional to the weight of the animal. The median lethal dose for each species, or the dose required to kill 50 per cent of the animals within forty-five days (beta rays) and twenty-one days (gamma rays) after exposure was found to be as follows: Baby rats were the most susceptible, the dose required being 2,200 beta rep or 510 gamma r. Rabbits were the most resistant, the dose required being 1,700 beta rep or 1,500 gamma r.

A series of experiments were performed with mice to determine the rate and pattern of recovery from total surface beta irradiation. It was found that by the split-dose technique, the recovery is at first very rapid with two-thirds of the effectiveness of the conditioning dose having been lost at the end of the third day and complete recovery having been attained by the end of the eighth day. There was also found to be an, as yet unexplained, over-recovery so that after the eighth day it required more than the standard test dose (4,700 rep) to kill 50 per cent of the animals in forty-five days. It was also found that single sublethal total surface doses of beta rays induced the formation of tumors in significant incidence in mice and rats, but produced none in either guinea pigs or rabbits.—*Robert K. Arbuckle, M.D.*

Tansley, Katharine, and Wilson, C. W. Irradiation of experimental cerebral tumors. *Radiology*, July, 1947, *49*, 62–71.

The authors produced experimental tumors in mice, both sarcomata and gliomata, by the introduction of methycholanthrene powder into the brain. Tumors were preserved by grafting pieces of their tissue into the brains of other young mice.

The brains of 39 mice were irradiated. All had gliomata grafted from the same original tumor. The half-value layer of radiation was 0.95 mm. Cu. The distance from focus spot to center of the mouse brain was 25 cm. Doses ranged from1,623 r to 3,247 r. The mean dose rate was 154 r/min.

The effect of irradiation on the growth of the tumors was quite variable. In some the largest dose had no effect, while in others the tumor

decreased in size or disappeared temporarily. In no case was the tumor entirely destroyed. The *average* result (as measured either by the survival time or by the number of animals showing regression of the tumor) was at least as good with 2,434 r as with 3,247 r.

Several animals died suddenly during or shortly after irradiation; postmortem examination revealed fresh and extensive hemorrhage from the tumor tissue.—*Arthur A. Brewer, M.D.*

Chalecke, William E., Jones, Glenn E., Miller, Leon L., Steinhausen, Theodore B., and Strain, William H. Iodinated organic compounds as contrast media for radiographic diagnoses. vi. *Radiology*, August, 1947, *49*, 131–136.

The authors report the results of experimental use of a 50 per cent emulsion of pantopaque (ethyl iodophenylundecylate) for retrograde pyelography and cystography, hysterosalpingography and intravenous injections, and a 70 per cent emulsion for bronchography in dogs. Both emulsions are readily injected through needles and catheters of small bore. The emulsions are prepared with the aid of a surface active agent (oleyl methyl taurine) and have the property of coating and adhering to mucosal surfaces.

The illustrations of the bronchograms of dogs are striking and show excellent detail of the bronchial branches. Films were made at intervals of five to ten minutes after instillation. Distribution is good and apparently little affected by this time interval. Emulsion is seen in the smaller radicles on the day following the original study. No definite toxic reactions have been observed. The illustrations of retrograde pyelographic studies are also excellent. Delineation of the calyces was present for some time after the medium had run out, in some instances several days. It is uncertain whether these emulsions are suitable for intravenous work.—*Chauncey N. Borman, M.D.*

George, Murray P., Mahoney, Earle B., Pearse, Herman E., and Strain, William H. Iodinated organic compounds as contrast media for radiographic diagnoses. vii. *Radiology*, August, 1947, *49*, 137–142.

The authors report clinical tests of the use of 50 per cent emulsion of iodophenylundecylate for visualization of light empyema cavities. This emulsion has the property of coating and adhering to the walls of a cavity, producing a more perfect delineation than is obtained with other solutions. The medium is distributed to all parts of the cavity by respiratory movements, posturing is not necessary and it is easily and completely removed by saline lavage. If a coagulum of pus is present the medium tends to collect on the surface of the coagulum. Relatively small amounts of the medium are required with a minimum of discomfort to the patients and no toxic reactions have been observed.—*Chauncey N. Borman, M.D.*

Jones, Glenn E., Chalecke, William E., Dec, Joseph, Schilling, John A., Ramsey, George H., Robertson, Harold D., and Strain, William H. Iodinated organic compounds as contrast media for radiographic diagnosis. viii. *Radiology*, August, 1947, *49*, 143–151.

Suspensions of tetraiodophthalimidoethanol were administered to dogs with experimentally produced marginal ulcers and more complete and more accurate delineation of the lesions was noted when compared to the appearance with barium sulphate suspensions. Additional advantages which are claimed for the new contrast medium are greater palatability, no increase in toxicity and less tendency to settle. Double contrast enemas in dogs were also more satisfactory with the iodinated medium than with barium sulphate.—*J. N. Ané, M.D.*

Halberstaedter, L., and Ickowicz, M. The early effects of x-rays on the ovaries of the rat. *Radiology*, April, 1947, *48*, 369–373.

As regards alterations in the ovary in the first few hours following irradiation, a diversity of opinion exists.

Histologic examinations of ovaries of normal and irradiated rats were made to determine whether any difference was present in the distribution of the pyknoses in the follicles.

The histologic studies were performed on ovaries of the following groups of highly inbred albino rats.

A. Control group: 4 rats.
B. Experimental groups: Rats irradiated with 50 to 2,000 r.
   (a) Seven rats, irradiated in the region of the abdomen, the ovaries being exposed directly to the action of the roentgen rays.

(b) Two rats, irradiated in the region of the cephalothorax, the ovaries being protected from direct exposure by means of a lead plate.

(c) Two young rats, irradiated totally.

The radiation was delivered from a Machlett therapy roentgen tube, operated on a multivolt apparatus at 150 kv., 4 ma., 0.5 mm. Al filter, distance 30 cm., 100 r per minute.

The animals were killed four hours after irradiation. Ovaries were fixed in Bouin's fluid and sectioned after embedding in paraffin.

In non-irradiated ovaries pyknoses are largely restricted to follicles whose ovules are in a state of division. When the follicles are examined in entirety, it becomes evident that pyknoses are normally very rare in the granular layer of follicles whose ovule contains a nucleus in a resting state. They are numerous in follicles whose ovule contains a nucleus in a state of division. The evaluation of the effect of roentgen rays on the ovary is best made, therefore, on the basis of findings in follicles which contain an ovule with a resting nucleus.

Observations have shown that four hours following irradiation numerous pyknoses are evident in the granular layer of the large follicles irrespective of whether the nucleus of the ovule is in a state of division or rest. Pyknoses were found, moreover, in follicular cells of young follicles in rats which had been irradiated, but never in corresponding follicles of non-irradiated rats. Follicles whose ovule is in a state of division show pyknoses in cells of the granular layer more frequently after irradiation than normally. A sufficient dose of roentgen rays produces lesion of the ovaries of a rat as early as four hours after irradiation.

The results were best defined with doses of 2,000 r delivered in the abdominal region. A pronounced pyknotic lesion was also observed in the rat which received 400 r in the abdominal region. The reaction of the ovary is not the same when it is not directly exposed to the roentgen rays.

No demonstrable difference was found between ovaries irradiated with doses of 50 and 100 r and non-irradiated ovaries. Doses of this magnitude are probably too low to evoke pyknotic lesions in the ovary within an interval of four hours.

Four hours after irradiation with a sufficient dose of roentgen rays pyknoses are in evidence in follicles whose ovule contains a resting nucleus, as well as in primary follicles.—*Stephen N. Tager, M.D.*

Hamilton, J. G. The metabolism of the fission products and the heaviest elements. *Radiology*, September, 1947, *49*, 325–343.

An investigation of the assimilation, distribution, retention, and excretion of fission products and the heaviest elements in the rat has been conducted at the Crocker Radiation Laboratory of the University of California. In order to protect the personnel working in the field of atomic energy information was needed concerning the behavior of these radio-elements following their introduction into the body by the three major portals of entry, namely inhalation, oral ingestion, and through cuts and abrasions of the intact skin. The fission of uranium results in the production of thirty-four radioactive elements and there have been identified nearly two hundred radioactive isotopes of this large number of elements that arise from fission. Only one fission product, radioiodine, had been studied sufficiently to permit an evaluation of the amount that could be tolerated within the body without producing damage. A table is presented showing the metabolism of the principal members of the long-lived fission products and certain of the heaviest elements in man and the rat following parenteral and oral administration. Only five of the listed fission products are absorbed from the digestive tract to a significant degree (strontium, barium, tellurium, iodine, and cesium). Strontium and barium are deposited and retained to a high degree by the skeleton. Iodine is accumulated and retained by the thyroid. Tellurium shows some accumulation in the kidneys and blood with a rather rapid rate of release from these tissues. Cesium is distributed quite uniformly throughout all of the tissues, the greatest accumulation occurring in the muscle, and it is quite promptly excreted. The distribution of these five fission products following oral absorption is indistinguishable from their metabolism after parenteral administration and they were also found to be readily absorbed through the lung.

Many of the long-life fission products and the actinide elements are promptly deposited and show long retention in the skeleton. Radioautographs show that, with the exception of strontium, they are not deposited in the mineral structure of bone but rather appear to be localized in and adjacent to the osteoid matrix. Of

the fission products and actinide elements that are deposited in bone, all except possibly columbium are released at a very slow rate. This places them in the category of radium so far as retention in the skeleton is concerned. Some of them, particularly most fission products, have half-lives very much shorter than radium and they emit beta particles instead of alpha particles and this somewhat reduces their hazardous nature. Of the fission products and actinide elements which emit alpha products and which accumulate in the osteoid matrix, their disintegration will result in bombardment of the radiosensitive bone marrow.—*Robert K. Arbuckle, M.D.*

Chamorro, A. Bases biologiques d'une action associée des hormones et des rayons X sur la cellule cancérisée de certaines glandes, sous controle hormonal. (The biological bases of an associated action of hormones and roentgen rays on the cancerous cells of certain glands under hormonal control.) *Compt. rend. Soc. de biol.* January, 1948, *142*, 3–4.

Development of resistance to irradiation of a small fraction of cancerous cells is the explanation of the recurrence and ultimate metastasis of malignancies, especially in protracted types of therapy. To overcome this, a combination of hormonal and roentgen treatment seems to be rational for malignancies of glands directly or indirectly influenced by hormones. The po nt is to increase the radiosensitivity of these resistant cells by stimulating them to premitosis through hormonal therapy.

The dose of the hormone and the roentgen radiation administered depends on the type of the glandular malignancy. For example, in the case of the epithelioma of the mammary gland, give estrogen (natural or synthetic) 3 to 5 mg. per day plus 5 mg. of progesterone daily, for ten days. On the eighth day begin roentgen therapy and in six days give 900 to 1,200 r per field. Repeat this associated treatment four or five times. A rest of one to two weeks between each series of treatment is necessary.

The epitheliomas which can be thus benefited are those of the:

(1) Mammary glands (estrogen and progesterone);
(2) Prostate (propionate of testosterone 25 mg. daily for 14 days);
(3) Thyroid (thyrotropic hormone 200 U. C. per day for 14 days or propylthiouracil 25 to 50 mg. per day for 12 days);
(4) Ovary (gonadotropic hormones);
(5) Uterus (estrogen plus progesterone);
(6) Submaxillary glands (androgen);
(7) Hypophysis (estrogen).—*J. N. Sarian, M.D.*

Landauer, Robert S. Application of the inverse-square law to oil-immersed tubes. *Radiology*, February, 1947, *48*, 175–177.

According to the inverse-square law, radiation intensity at a given point varies inversely as the square of the distance from the source. Two prerequisites are included but often overlooked: (1) that radiation be emitted from a point source, (2) that no absorbing or scattering media intervene between the source and the site in question.

In view of the doubt expressed regarding the validity of this law as applied to small oil-immersed tubes (140 kv., peak, or less) radiation intensity determinations were made at various levels, between 5 and 20 inches, using a Victoreen r-meter and a specially built wooden structure. Eleven different tubes were tested. The averages obtained indicate that the inverse-square law may be applied in calculating intensities at distances between 5 and 20 inches with an average error of not over 1 per cent, and a maximum error of ± 6 per cent.—*William H. Shehadi, M.D.*

Trout, E. D., and Atlee, Z. J. Low-absorption roentgen-ray measurements from 500 to 1,000 kilovolts. *Radiology*, June, 1947, *48*, 604–609.

An extension of earlier studies is presented on low-absorption roentgen-ray measurements using a beryllium window, permanently evacuated tube, at voltages up to 1,000 kv.

A multisection million volt tube with beryllium window of $1\frac{1}{4}$ inches diameter and inherent filtration of 3 mm. of beryllium (equivalent to about 0.05 mm. of lead) was used. All measurements were made with a Victoreen thimble chamber at 100 cm. distance, 500 to 1,000 kv., and 0.1 ma. to 3.0 ma. Because of filament space-charge limitations, a maximum of 500 kv. at 1.0 ma. was used. Absorption data were taken for copper and lead.

Results are given in the form of graphs showing absorption curves for copper and lead, half-value layers in lead and a graph for determining the inherent filtration from the half-value layer in lead for voltages of 500 to 1,000 kv. The half-value layer at 1,000 kv. with no added filtration was 1.1 mm. of lead as against

1.9 mm. for the conventional million volt tube.

Examples of output obtainable from this tube were as follows: (1) at 1,000 kv. and 3 ma. (the full load rating), at 50 cm. distance, 264 r per minute, (2) at 2 cm. distance, in contact with the beryllium window, 165,000 r per minute.

A graph for determining inherent filtration from the half-value layer in lead of any roentgen tube operating in the range of 500 to 1,000 kv. is presented.

The authors are of the opinion that beryllium windows are indicated for tubes operating up to 750 kv. but that at and above 1,000 kv., emphasis should be placed on the window thinness rather than its composition.—*E. D. Hudack, M.D.*

Rogers, T. H. High-intensity radiation from beryllium-window x-ray tubes. *Radiology*, June, 1947, *48*, 594–603.

Beryllium has the lowest absorption coefficient of any material likely to be used for windows in roentgen tubes. Originally beryllium was used in the internal hoods of roentgen tubes to stop secondary electrons while allowing the transmission of roentgen rays.

The first commercially produced tubes with vacuum-tight beryllium windows were designed primarily for roentgen-ray diffraction where the use of long wavelengths necessitated reduction of window absorption to a minimum. The low-absorption window with its advantages soon lent itself to use in microphotography and industrial work. As these tubes became used more widely, a demand arose for beryllium window roentgen tubes with larger windows. Aside from permitting a greater afflux, beryllium can be located very close to the focal spot. This is not feasible with other low-absorption materials. An intensity of 2,330,000 r per minute is obtainable at 2 cm. (target face to outer surface of window) at 50 kv. and 20 ma.

These high outputs lend themselves to new exploits such as: (1) sterilization of vaccines while the antibodies remain unaffected, (2) sterilization of suture material without heating, (3) sterilization of foods without subjecting them to flavor destroying temperatures. In therapeutic radiology while the high intensity in itself is not directly an advantage, it does afford a wide range of dosage rates in its application to intracavitary, "grenz" ray and "skin therapy." The possible role this achievement may play in atomic research and industry is alluded to. Several specific photochemical reactions are mentioned, in which the color changes in precious stones and the fluorescence in other substances can be used for qualitative and quantitative analysis in research.

Suitability of various instruments for measuring the r per minute output of the radiation is discussed and references to the literature discoursing on these instruments are cited.

A tube of new design, constructed on an experimental basis making all the radiation available in the continuous processing of materials is discussed. This tube has a domed window which makes possible a 180 degree radiation field. It is operable with a load of 60 kv. at 100 ma. with a predicted output of approximately 5,000,000 r per minute available over 25 sq. cm. —*E. D. Hudack, M.D.*

Mallet, Lucien, and Maurin, Robert. A study of quality and origin of parasitic radiation from the target of an x-ray tube. *Radiology*, June, 1947, *48*, 628–632.

The studies were made on a machine of the United States Army Field Unit type. It was found that roentgen rays were produced not only at the principal focal point but also on the remainder of the tungsten target and the copper stem. The intensity and quality of the radiation from these zones were studied by three methods: (1) independent micro-ionization chambers, (2) the Strauss dosimeter, (3) blackening of a film. It was found that radiation from the principal focal point was of the greatest wavelength, whereas rays from the periphery of the target and the supporting stem were more penetrating. The radiation was most penetrating at the point of exit from the tube when a limiting diaphram with a large aperture was used.

The details of the experiments are clearly described and the explanations of the phenomena are graphically illustrated. These findings are of significance for both roentgenography and radiotherapy.—*Oliver P. Winslow, Jr., M.D.*

Lange, Kurt, and Evans, Robley D. Absorption of radon through the skin and its exhalation through the lungs. *Radiology*, May, 1947, *48*, 514–516.

The authors describe their method of measuring the absorption of radon through the skin and its exhalation through the lungs in 3 patients under treatment with radon ointment. Their method is convenient and yet practical,

and they found that appreciable amounts of radon gas applied in ointments were absorbed through the intact skin and through opened wounds and affected deeper structures by absorption into the blood stream and thence transportation by the blood stream to the deeper tissues. They thus state that the efficiency of radon ointment in the supplying radon and its alpha irradiation to underlying tissues is quite high.—*Moris Horwitz, M.D.*

Jacobson, Leon O., and Marks, E. K. The hematological effects of ionizing radiations in the tolerance range. *Radiology*, September, 1947, *49*, 286–298.

Knowledge of the biological effects of radiations in general and of certain radiations and radioactive materials specifically was so superficial prior to World War II that the medical and biological divisions of the Plutonium Project were organized. The objectives were essentially to study the fundamental and comparative action of radiations and radioactive materials and to apply these findings to the protection of personnel or individuals potentially in danger of exposure to these physical hazards. Data were required on the biological effect of chronic irradiation in the region of the "tolerance dose." Externally originating radiation, "whole body," had to do with gamma rays, roentgen rays, beta rays, and neutrons. This study presents data on the findings in the peripheral blood of animals exposed to roentgen rays and gamma rays. Rabbits, mice, and guinea pigs were used. Blood studies included erythrocytes, hemoglobin, leukocytes, the differential leukocyte count, platelets, reticulocytes, and in special instances erythrocyte diameter. After control preirradiation exposure counts were made at least twice, the animals were placed in cages in fixed positions to receive definite exposures of deliberately planned irradiation from a large centrally placed radium source. The species and substrains of laboratory animals were divided into groups and exposed to doses of 0.1, 1.1, 2.2, 4.4, and 8.8 r, some for eight hours per day and others for twenty-four hours per day, six days weekly. The animals were observed while thus exposed over periods now well extended beyond three years.

Significant Findings

1. In female mice, biological effects appear in the absence of detectable hematological change. Ovarian tumors developed in mice exposed to 0.1 and 1.1 r per day while no detectable changes in peripheral blood occurred at any time during the three years' exposure to these doses.

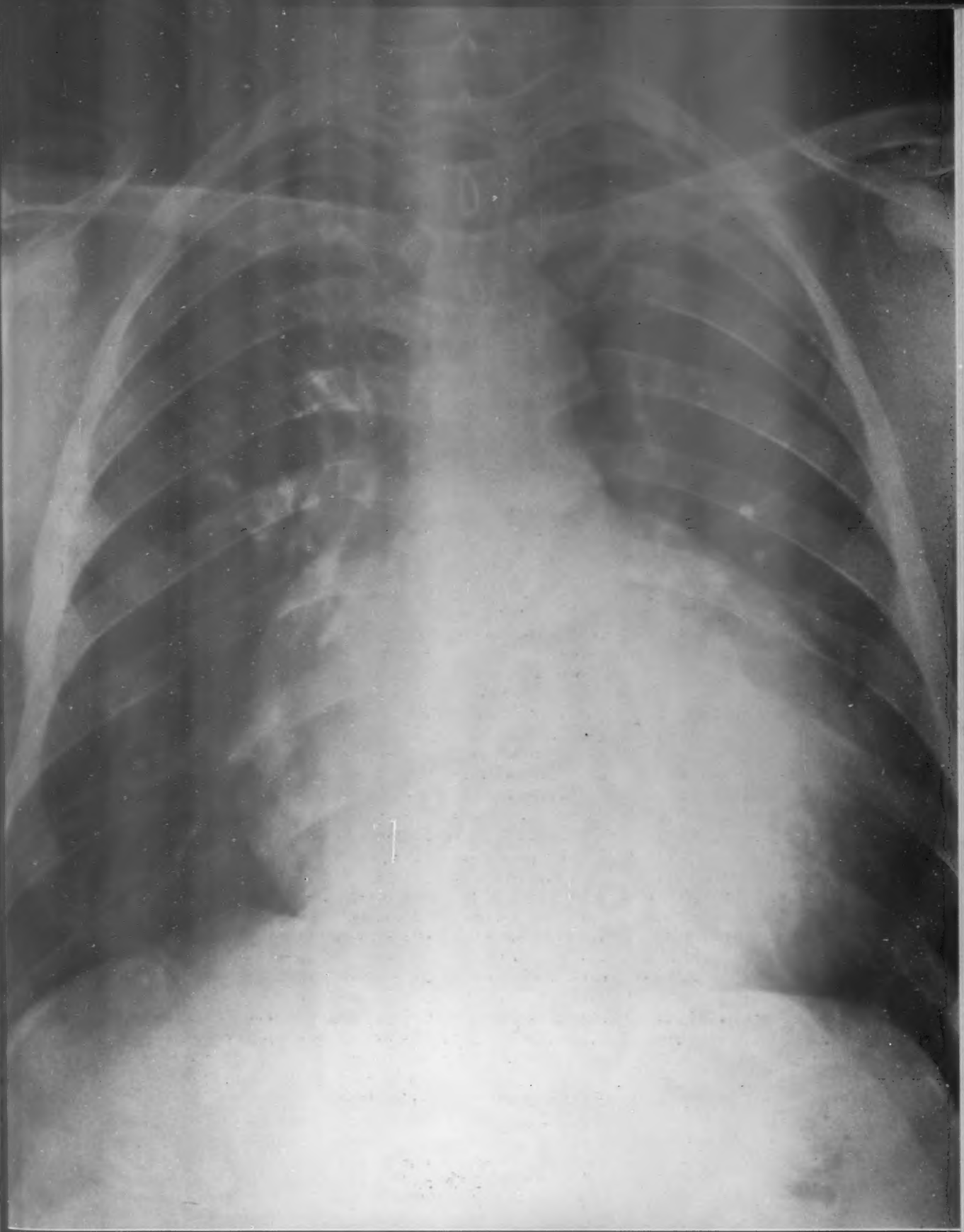
2. Findings commonly believed to indicate chronic irradiation damage (lymphocytosis, eosinophilia, monocytosis) did not occur in any of the three species exposed clinically to doses between 0.1 and 8.8 r per eight hour or twenty-four hour day.

3. Lymphocyte reduction was the earliest abnormality noted in the peripheral blood of these three species after chronic exposure.

4. There was no histologic evidence of abnormality of the blood-forming tissues in the animals which developed a lymphopenia.

5. Severe anemia (acute onset) was common cause of death of guinea pigs exposed in the 8.8 and 4.4 r exposure level.

The personnel of the Plutonium Project were divided into (1) control group and (2) work hazard group depending on whether or not their work brought them into exposure or potential exposure to physically hazardous materials. Frequent hematological studies were made in these groups (varied from daily to every three months). A leukocyte count of 3,000 per cubic millimeter called for careful special clinical and laboratory studies. Only relatively few instances were encountered in which changes in the peripheral blood of personnel could be attributed to contact with external radiation or the deposition of radioactive materials within the body, and no changes occurred which were referable to radiation exposure in the "tolerance range" of 0.1 r per day as set by the National Bureau of Standards.—*Robert K. Arbuckle, M.D.*



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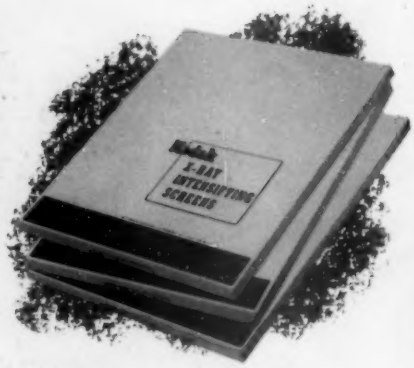

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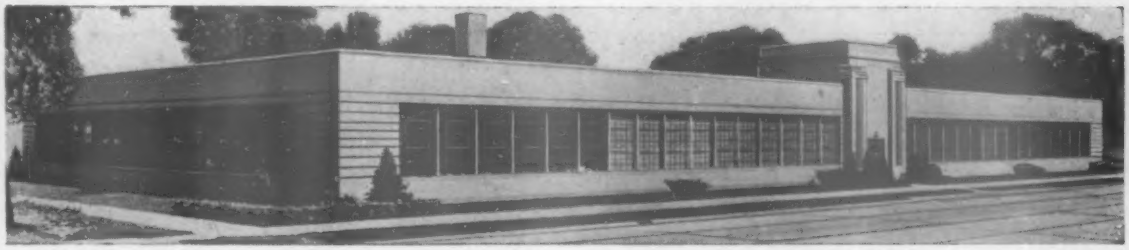

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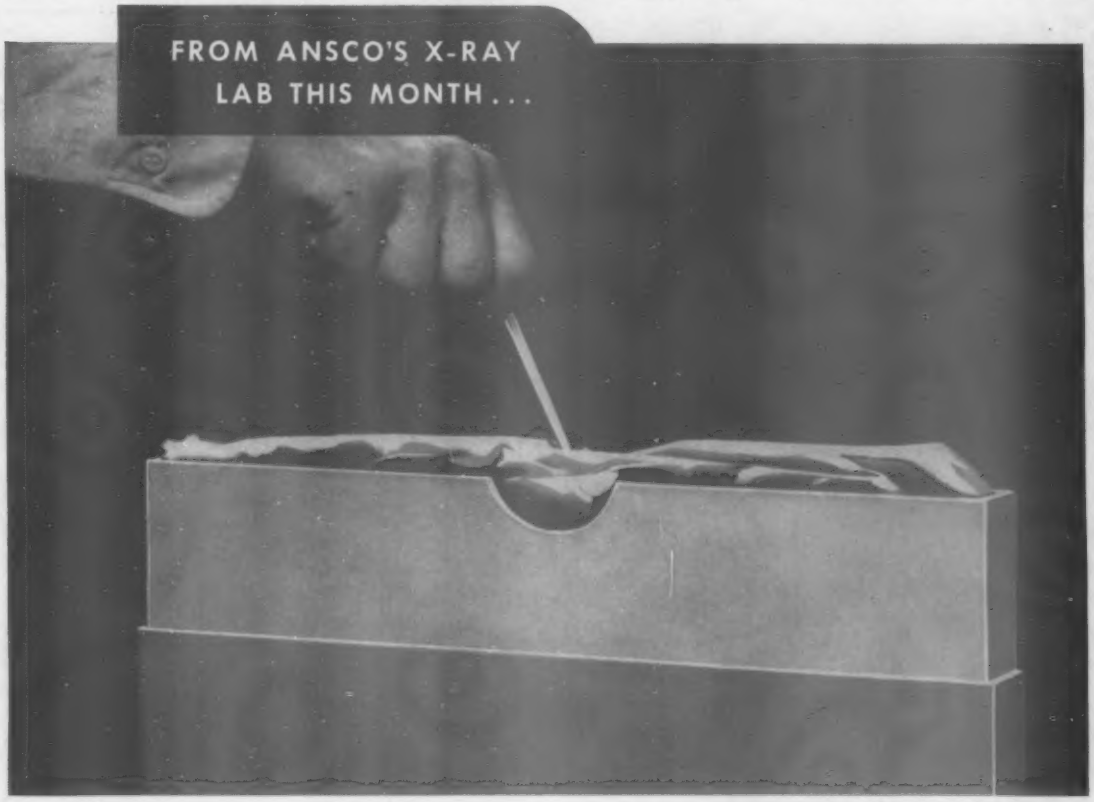

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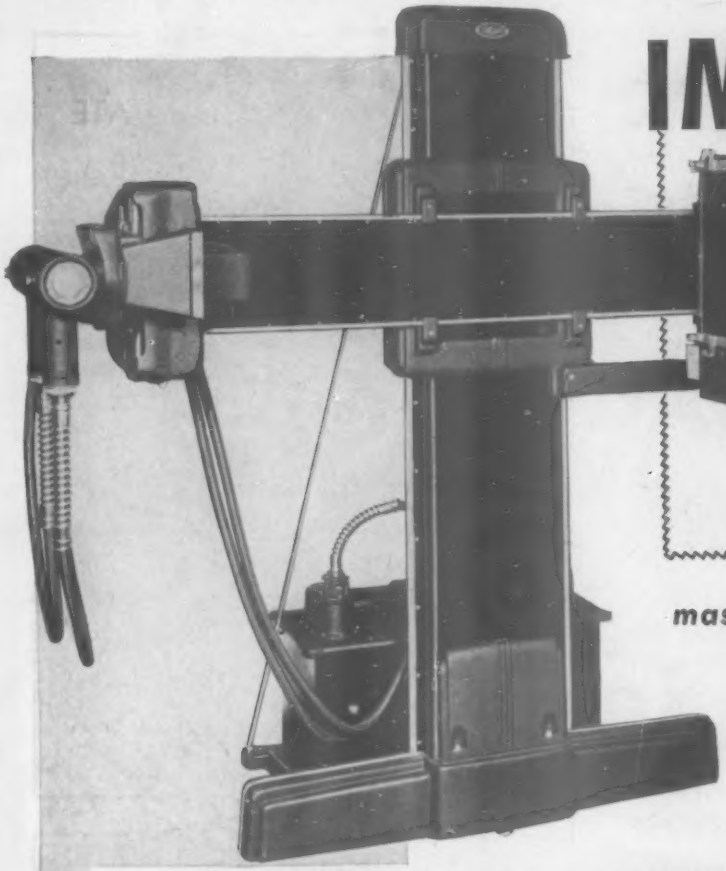

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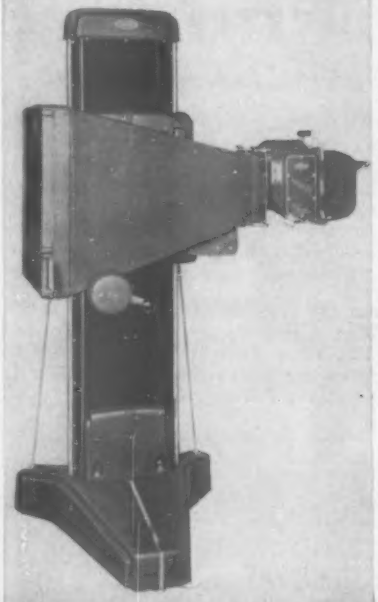

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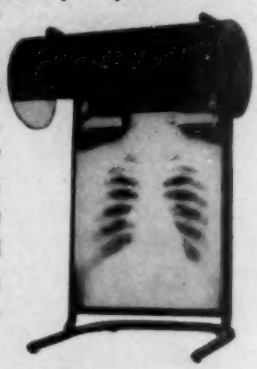

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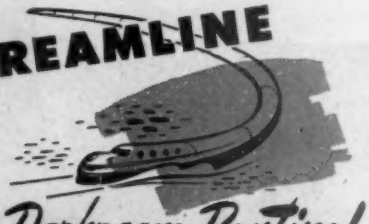

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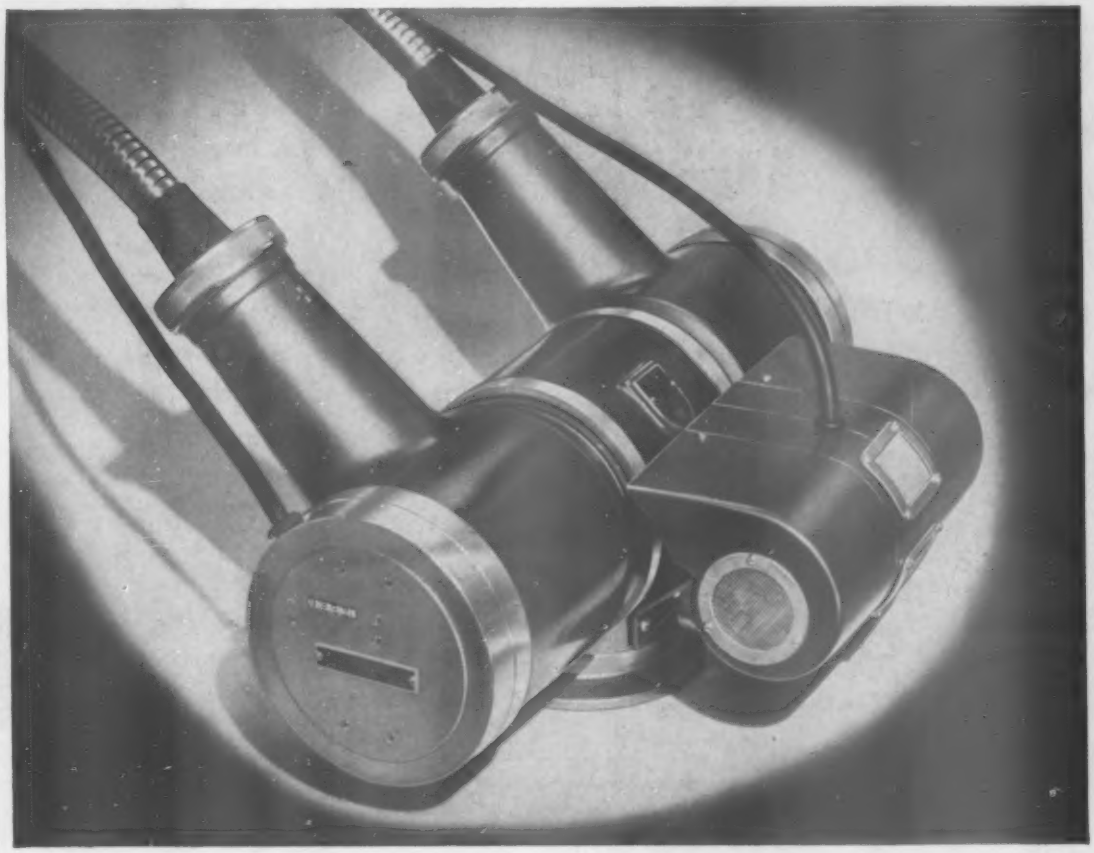

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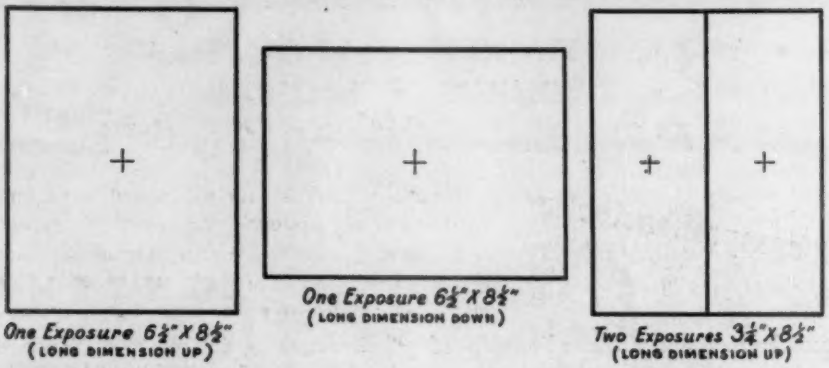

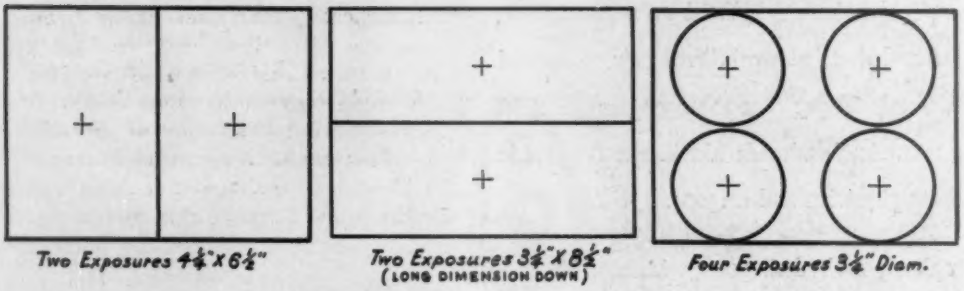

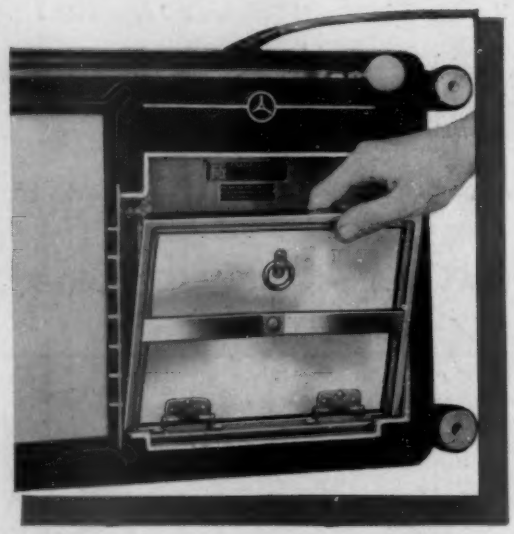

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